(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 2 487 165 B1

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication and mention of the grant of the patent:
14.09.2016 Bulletin 2016/37

(21) Application number: **12167594.6**

(22) Date of filing: **06.07.2007**

(51) Int Cl.:
C07D 277/28 *(2006.01)* ***C07D 417/14*** *(2006.01)*
A61K 31/427 *(2006.01)* ***A61P 31/12*** *(2006.01)*

(54) **Modulators of pharmacokinetic properties of therapeutics**

Modulatoren der pharmakokinetischen Eigenschaften von Therapeutika

Modulateurs de propriétés pharmacocinétiques d'agents thérapeutiques

(84) Designated Contracting States:
AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IS IT LI LT LU LV MC MT NL PL PT RO SE SI SK TR
Designated Extension States:
AL BA HR MK RS

(30) Priority: **23.02.2007 US 903228 P**
21.07.2006 US 832371 P
07.07.2006 US 819315 P

(43) Date of publication of application:
15.08.2012 Bulletin 2012/33

(60) Divisional application:
16180602.1

(62) Document number(s) of the earlier application(s) in accordance with Art. 76 EPC:
07836007.0 / 2 049 506

(73) Proprietor: **GILEAD SCIENCES, INC.**
Foster City,
California 94404 (US)

(72) Inventors:
- **Desai, Manoj, C.**
  Pleasant Hill, CA California 94523 (US)
- **Hong, Allen, Yu**
  San Jose, CA California 95129 (US)
- **Liu, Hongtao**
  Cupertino, CA California 95014 (US)
- **Xu, Lianhong**
  Palo Alto, CA California 94303 (US)
- **Vivian, Randall, W.**
  San Mateo, CA California 94404 (US)

(74) Representative: **Hallybone, Huw George et al**
Carpmaels & Ransford LLP
One Southampton Row
London WC1B 5HA (GB)

(56) References cited:
EP-B- 1 183 026 **WO-A1-97/01349**

Note: Within nine months of the publication of the mention of the grant of the European patent in the European Patent Bulletin, any person may give notice to the European Patent Office of opposition to that patent, in accordance with the Implementing Regulations. Notice of opposition shall not be deemed to have been filed until the opposition fee has been paid. (Art. 99(1) European Patent Convention).

EP 2 487 165 B1

Description

FIELD OF THE INVENTION

[0001] This application relates generally to compounds and pharmaceutical compositions which modify, *e.g.*, improve, the pharmacokinetics of a co-administered drug, and their use in methods of modifying, *e.g.*, improving, the pharmacokinetics of a drug by co-administration of the compounds with the drug.

BACKGROUND OF THE INVENTION

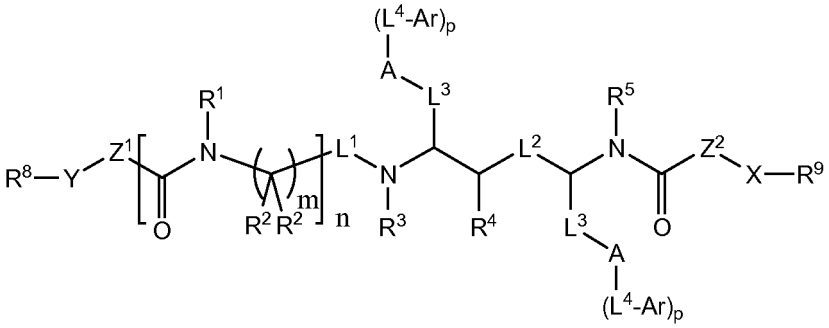
[0002] Oxidative metabolism by cytochrome P450 enzymes is one of the primary mechanisms of drug metabolism. It can be difficult to maintain therapeutically effective blood plasma levels of drugs which are rapidly metabolized by cytochrome P450 enzymes. Accordingly, the blood plasma levels of drugs which are susceptible to cytochrome P450 enzyme degradation can be maintained or enhanced by co-administration of cytochrome P450 inhibitors, thereby improving the pharmacokinetics of the drug.

[0003] While certain drugs are known to inhibit cytochrome P450 enzymes, more and/or improved inhibitors for cytochrome P450 monooxygenase are desirable. Particularly, it would be desirable to have cytochrome P450 monooxygenase inhibitors which do not have appreciable biological activity other than cytochrome P450 inhibition. Such inhibitors can be useful for minimizing undesirable biological activity, *e.g.*, side effects. In addition, it would be desirable to have P450 monooxygenase inhibitors that lack significant or have a reduced level of protease inhibitor activity. Such inhibitors could be useful for enhancing the effectiveness of antiretroviral drugs, while minimizing the possibility of eliciting viral resistance, especially against protease inhibitors.

SUMMARY OF THE INVENTION

[0004] One aspect of the present application is directed to compounds and pharmaceutical compositions which modify, *e.g.*, improve, the pharmacokinetics of a co-administered drug, *e.g.*, by inhibiting cytochrome P450 monooxygenase. The compounds and compositions covered by the invention are defined by the scope of the appended claims. Aspects disclosed herein which are not within the scope of the claims are provided for reference.

[0005] The present disclosure generally provides for compounds having a structure according to Formula I:



Formula I

or a pharmaceutically acceptable salt, solvate, and/or ester thereof, wherein,

L^1 is selected from the group consisting of $-C(R^6)_2-$, -C(O)-, $-S(O)_2-$, $-N(R^7)-C(O)-$, and -O-C(O)-;
L^2 is a covalent bond, $-C(R^6)_2-$ or -C(O)-;
each L^3 is independently a covalent bond, an alkylene, or substituted alkylene;
each L^4 is independently selected from the group consisting of a covalent bond, alkylene, substituted alkylene, -O-, $-CH_2-O-$, and -NH-;
each A is independently selected from the group consisting of H, alkyl, substituted alkyl, aryl, substituted aryl, heterocyclyl, and substituted heterocyclyl,
with the proviso that when A is H, p is 0;
Z^1 and Z^2 are each independently -O- or $-N(R^7)-$;
Y and X are independently selected from the group consisting of heterocyclyl and heterocyclylalkyl;
each Ar is independently selected from the group consisting of aryl, substituted aryl, heteroaryl, and substituted

heteroaryl;
R^1, R^3, and R^5 are each independently selected from the group consisting of H, alkyl, substituted alkyl, arylalkyl, and substituted arylalkyl;
each R^2 is independently selected from the group consisting of H, alkyl, substituted alkyl, alkoxyalkyl, hydroxyalkyl, arylheteroalkyl, substituted arylheteroalkyl, arylalkyl, substituted arylalkyl, heterocyclylalkyl, substituted heterocyclylalkyl, aminoalkyl, substituted aminoalkyl, -alkylene-C(O)-OH,-alkylene-C(O)-Oalkyl, -alkylene-C(O)amino, -alkylene-C(O)-alkyl;
R^4 and R^6 are independently selected from the group consisting of H, alkyl, substituted alkyl, and heteroalkyl;
each R^7 is independently selected from the group consisting of H, alkyl, substituted alkyl, heteroalkyl, carbocyclyl, substituted carbocyclyl, heterocyclyl, and substituted heterocyclyl;
R^8 and R^9 are each one or more substituents independently selected from the group consisting of H, alkyl, substituted alkyl, halogen, aryl, substituted aryl, heterocyclyl, substituted heterocyclyl, and -CN;
m is 1 or 2;
n is 0 or 1; and
each p is independently 0 or 1.

[0006] In another embodiment, the present application provides for a pharmaceutical composition comprising a compound of the invention, and a pharmaceutically acceptable carrier or excipient.

[0007] In another embodiment, the present application provides for a pharmaceutical composition comprising a compound of the invention, at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or excipient.

[0008] In another embodiment, the present application provides for a compound of the invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in a method for improving the pharmacokinetics of a drug.

[0009] In another embodiment, the present application provides for a compound of the invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450 monooxygenase, for use in a method for inhibiting cytochrome P450 monooxygenase in a patient.

[0010] In another embodiment, the present application provides fora compound of the invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents which are metabolized by cytochrome P450 monooxygenase, and are suitable for treating a viral infection, *e.g.*, HIV for use in a method for treating a viral infection, *e.g.*, HIV.

[0011] In another embodiment, the present application provides for a combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of the invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof; and
b) a second pharmaceutical composition comprising at least one additional active agent which is metabolized by cytochrome P450 monooxygenase.

DETAILED DESCRIPTION

Definitions

[0012] Unless stated otherwise, the following terms and phrases as used herein are intended to have the following meanings:

When trade names are used herein, applicants intend to independently include the tradename product and the active pharmaceutical ingredient(s) of the tradename product.

[0013] As used herein, "a compound of the invention" means a compound defined in the claims or a pharmaceutically acceptable salt, solvate, ester or stereoisomer thereof. Similarly, with respect to isolatable intermediates, the phrase "a compound of formula (number)" means a compound of that formula and pharmaceutically acceptable salts, solvates and physiologically functional derivatives thereof.

[0014] "Alkyl" is hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms. For example, an alkyl group can have 1 to 20 carbon atoms (*i.e,* C_1-C_{20} alkyl), 1 to 10 carbon atoms (*i.e.,* C_1-C_{10} alkyl), or 1 to 6 carbon atoms (*i.e.,* C_1-C_6 alkyl). Examples of suitable alkyl groups include, but are not limited to, methyl (Me, $-CH_3$), ethyl (Et, $-CH_2CH_3$), 1-propyl (n-Pr, n-propyl, $-CH_2CH_2CH_3$), 2-propyl (i-Pr, i-propyl, $-CH(CH_3)_2$), 1-butyl (n-Bu, n-butyl, $-CH_2CH_2CH_2CH_3$), 2-methyl-1-propyl (i-Bu, i-butyl, $-CH_2CH(CH_3)_2$), 2-butyl (s-Bu, s-butyl, $-CH(CH_3)CH_2CH_3$), 2-methyl-2-propyl (t-Bu, t-butyl, $-C(CH_3)_3$), 1-pentyl (n-pentyl, $-CH_2CH_2CH_2CH_2CH_3$), 2-pentyl ($-CH(CH_3)CH_2CH_2CH_3$), 3-pentyl ($-CH(CH_2CH_3)_2$), 2-methyl-2-butyl ($-C(CH_3)_2CH_2CH_3$), 3-methyl-2-butyl ($-CH(CH_3)CH(CH_3)_2$), 3-methyl-1-butyl ($-CH_2CH_2CH(CH_3)_2$), 2-methyl-1-butyl ($-CH_2CH(CH_3)CH_2CH_3$), 1-hexyl ($-CH_2CH_2CH_2CH_2CH_2CH_3$), 2-hexyl

(-CH(CH_3)$CH_2CH_2CH_2CH_3$), 3-hexyl (-CH(CH_2CH_3)($CH_2CH_2CH_3$)), 2-methyl-2-pentyl (-C(CH_3)$_2CH_2CH_2CH_3$), 3-methyl-2-pentyl (-CH(CH_3)CH(CH_3)CH_2CH_3), 4-methyl-2-pentyl (-CH(CH_3)CH_2CH(CH_3)$_2$), 3-methyl-3-pentyl (-C(CH_3)(CH_2CH_3)$_2$), 2-methyl-3-pentyl (-CH(CH_2CH_3)CH(CH_3)$_2$), 2,3-dimethyl-2-butyl (-C(CH_3)$_2$CH(CH_3)$_2$), 3,3-dimethyl-2-butyl (-CH(CH_3)C(CH_3)$_3$, and octyl (-$(CH_2)_7CH_3$).

[0015] "Alkoxy" means a group having the formula -O-alkyl, in which an alkyl group, as defined above, is attached to the parent molecule via an oxygen atom. The alkyl portion of an alkoxy group can have 1 to 20 carbon atoms (*i.e.,* C_1-C_{20} alkoxy), 1 to 12 carbon atoms(*i.e.*, C_1-C_{12} alkoxy), or 1 to 6 carbon atoms(*i.e.*, C_1-C_6 alkoxy). Examples of suitable alkoxy groups include, but are not limited to, methoxy (-O-CHs or -OMe), ethoxy (-OCH_2CH_3 or -OEt), t-butoxy (-O-C(CH_3)$_3$ or -OtBu) and the like.

[0016] "Haloalkyl" is an alkyl group, as defined above, in which one or more hydrogen atoms of the alkyl group is replaced with a halogen atom. The alkyl portion of a haloalkyl group can have 1 to 20 carbon atoms (*i.e.,* C_1-C_{20} haloalkyl), 1 to 12 carbon atoms(*i.e.*, C_1-C_{12} haloalkyl), or 1 to 6 carbon atoms(*i.e.*, C_1-C_6 alkyl). Examples of suitable haloalkyl groups include, but are not limited to, -CF_3, -CHF_2, -CFH_2, -CH_2CF_3, and the like.

[0017] "Alkenyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e*. a carbon-carbon, sp^2 double bond. For example, an alkenyl group can have 2 to 20 carbon atoms (*i.e.,* C_2-C_{20} alkenyl), 2 to 12 carbon atoms (*i.e.,* C_2-C_{12} alkenyl), or 2 to 6 carbon atoms (*i.e.,* C_2-C_6 alkenyl). Examples of suitable alkenyl groups include, but are not limited to, ethylene or vinyl (-CH=CH_2), allyl (-CH_2CH=CH_2), cyclopentenyl (-C_5H_7), and 5-hexenyl (-$CH_2CH_2CH_2CH_2$CH=CH_2).

[0018] "Alkynyl" is a hydrocarbon containing normal, secondary, tertiary or cyclic carbon atoms with at least one site of unsaturation, *i.e*. a carbon-carbon, sp triple bond. For example, an alkynyl group can have 2 to 20 carbon atoms (*i.e.,* C_2-C_{20} alkynyl), 2 to 12 carbon atoms (*i.e.,* C_2-C_{12} alkyne,), or 2 to 6 carbon atoms (*i.e.,* C_2-C_6 alkynyl). Examples of suitable alkynyl groups include, but are not limited to, acetylenic (-C≡CH), propargyl (-CH_2C≡CH), and the like.

[0019] "Alkylene" refers to a saturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkane. For example, an alkylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkylene radicals include, but are not limited to, methylene (-CH_2-), 1,1-ethyl (-CH(CH_3)-), 1,2-ethyl (-CH_2CH_2-), 1,1-propyl (-CH(CH_2CH_3)-), 1,2-propyl (-CH_2CH(CH_3)-), 1,3-propyl (-$CH_2CH_2CH_2$-), 1,4-butyl (-$CH_2CH_2CH_2CH_2$-), and the like.

[0020] "Alkenylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkene. For example, and alkenylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkenylene radicals include, but are not limited to, 1,2-ethylene (-CH=CH-).

[0021] "Alkynylene" refers to an unsaturated, branched or straight chain or cyclic hydrocarbon radical having two monovalent radical centers derived by the removal of two hydrogen atoms from the same or two different carbon atoms of a parent alkyne. For example, an alkynylene group can have 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. Typical alkynylene radicals include, but are not limited to, acetylene (-C≡C-), propargyl (-CH_2C≡C-), and 4-pentynyl (-$CH_2CH_2CH_2$C≡CH-).

[0022] "Amino" means an -NH_2 or a -NR_2 group in which the "R" groups are independently H, alkyl, carbocyclyl (substituted or unsubstituted, including saturated or partially unsaturated cycloalkyl and aryl groups), heterocyclyl (substituted or unsubstituted, including saturated or unsaturated heterocycloalkyl and heteroaryl groups), arylalkyl (substituted or unsubstituted) or arylalkyl (substituted or unsubstituted) groups. Non-limiting examples of amino groups include -NH_2, -NH(alkyl), -NH(carbocyclyl), -NH(heterocyclyl), -N(alkyl)$_2$, -N(carbocyclyl)$_2$, -N(heterocyclyl)$_2$, -N(alkyl)(carbocyclyl), -N(alkyl)(heterocyclyl), -N(carbocyclyl)(heterocyclyl), etc., wherein alkyl, carbocyclyl, and heterocyclyl can be substituted or unsubstituted and as defined and described herein. "Substituted" or "protected" amino means an aminoalkyl as described and defined herein in which a H of the amino group is replaced with e.g., acyl groups, for example conventional amine protecting groups such as 9-Fluorenylmethyl carbamate ("Fmoc"), *t*-Butyl carbamate ("Boc"), Benzyl carbamate ("Cbz"), acetyl, trifluoracetyl, phthalimidyl, triphenylmethyl, *p*-Toluenesulfonyl ("Tosyl"), methylsulfonyl ("mesyl"), etc.

[0023] "Aminoalkyl" means an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an amino radical as defined and described herein. Non-limiting examples of aminoalkyl include -CH_2-NH_2, -CH_2CH_2-NH_2, -$CH_2CH_2CH_2$-NH_2, -$CH_2CH_2CH_2CH_2$-NH_2, -CH_2CH(CH_3)-NH_2, -CH_2CH_2CH(CH_3)-NH_2, -CH_2-NH(CH_3), -CH_2CH_2-NH(CH_3), -$CH_2CH_2CH_2$-NH(CH_3), -$CH_2CH_2CH_2CH_2$-NH(CH_3), -CH_2CH(CH_3)-NH(CH_3), -CH_2CH_2CH(CH_3)-NH(CH_3), -CH_2-N(CH_3)$_2$, -CH_2CH_2-N(CH_3)$_2$, -$CH_2CH_2CH_2$-N(CH_3)$_2$, -$CH_2CH_2CH_2CH_2$-N(CH_3)$_2$, -CH_2CH(CH_3)-N(CH_3)$_2$, -CH_2CH_2CH(CH_3)-N(CH_3)$_2$, -CH_2-NH(CH_2CH_3), -CH_2CH_2-NH(CH_2CH_3), -$CH_2CH_2CH_2$-NH(CH_2CH_3), -$CH_2CH_2CH_2CH_2$-NH(CH_2CH_3), -CH_2CH(CH_3)-NH(CH_2CH_3), -CH_2CH_2CH(CH_3)-NH(CH_2CH_3), -CH_2-N(CH_2CH_3)$_2$, -CH_2CH_2-N(CH_2CH_3)$_2$, -$CH_2CH_2CH_2$-N(CH_2CH_3)$_2$, -$CH_2CH_2CH_2CH_2$-N(CH_2CH_3)$_2$, -CH_2CH(CH_3)-N(CH_2CH_3)$_2$, -CH_2CH_2CH(CH_3)-N(CH_2CH_3)$_2$, etc. "Substituted" or "protected" aminoalkyl means an aminoalkyl as described and defined herein in which the H of the amino group is replaced with e.g., acyl groups, for example conventional amine

protecting groups such as 9-Fluorenylmethyl carbamate ("Fmoc"), *t*-Butyl carbamate ("Boc"), Benzyl carbamate ("Cbz"), acetyl, trifluoracetyl, phthalimidyl, triphenylmethyl, *p*-Toluenesulfonyl ("Tosyl"), methylsulfonyl ("mesyl"), etc.

[0024] "Aryl" means an aromatic hydrocarbon radical derived by the removal of one hydrogen atom from a single carbon atom of a parent aromatic ring system. For example, an aryl group can have 6 to 20 carbon atoms, 6 to 14 carbon atoms, or 6 to 12 carbon atoms. Typical aryl groups include, but are not limited to, radicals derived from benzene (e.g., phenyl), substituted benzene, naphthalene, anthracene, biphenyl, and the like.

[0025] "Arylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with an aryl radical. Typical arylalkyl groups include, but are not limited to, benzyl, 2-phenylethan-1-yl, naphthylmethyl, 2-naphthylethan-1-yl, naphthobenzyl, 2-naphthophenylethan-1-yl and the like. The arylalkyl group can comprise 6 to 20 carbon atoms, *e.g.*, the alkyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

[0026] "Arylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp^2 carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkenyl can include, for example, any of the aryl groups disclosed herein, and the alkenyl portion of the arylalkenyl can include, for example, any of the alkenyl groups disclosed herein. The arylalkenyl group can comprise 6 to 20 carbon atoms, *e.g.*, the alkenyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

[0027] "Arylalkynyl" refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with an aryl radical. The aryl portion of the arylalkynyl can include, for example, any of the aryl groups disclosed herein, and the alkynyl portion of the arylalkynyl can include, for example, any of the alkynyl groups disclosed herein. The arylalkynyl group can comprise 6 to 20 carbon atoms, *e.g.*, the alkynyl moiety is 1 to 6 carbon atoms and the aryl moiety is 6 to 14 carbon atoms.

[0028] The term "substituted" in reference to alkyl, alkylene, aryl, arylalkyl, heterocyclyl, heteroaryl, carbocyclyl, etc., for example, "substituted alkyl", "substituted alkylene", "substituted aryl", "substituted arylalkyl", "substituted heterocyclyl", and "substituted carbocyclyl" means alkyl, alkylene, aryl, arylalkyl, heterocyclyl, carbocyclyl respectively, in which one or more hydrogen atoms are each independently replaced with a non-hydrogen substituent. Typical substituents include, but are not limited to, -X, -R, -O-, =O, -OR, -SR, -S-, $-NR_2$, $-N^+R_3$, =NR, $-CX_3$, -CN, -OCN, -SCN, -N=C=O, -NCS, -NO, $-NO_2$, $=N_2$, $-N_3$,NHC(=O)R, -NHS(=O)$_2$R, -C(=O)R, -C(=O)NRR -S(=O)$_2$O-, -S(=O)$_2$OH, -S(=O)$_2$R,OS(=O)$_2$OR, -S(=O)$_2$NR, -S(=O)R, -OP(=O)(OR)$_2$, -P(=O)(OR)$_2$, -P(=O)(O-)$_2$, -P(=O)(OH)$_2$, -P(O)(OR)(O-), -C(=O)R, -C(=O)OR, -C(=O)X, -C(S)R, -C(O)OR, -C(O)O-, -C(S)OR, -C(O)SR, -C(S)SR, -C(O)NRR, -C(S)NRR, -C(=NR)NRR, where each X is independently a halogen: F, Cl, Br, or I; and each R is independently H, alkyl, aryl, arylalkyl, a heterocycle, or a protecting group or prodrug moiety. Alkylene, alkenylene, and alkynylene groups may also be similarly substituted. When the number of carbon atoms is designated for a substituted group, the number of carbon atoms refers to the group, not the substituent (unless otherwise indicated). For example, a C_{1-4} substituted alkyl refers to a C_{1-4} alkyl, which can be substituted with groups having more the, e.g., 4 carbon atoms.

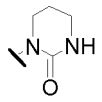
[0029] The term "prodrug" as used herein refers to any compound that when administered to a biological system generates the drug substance, i.e., active ingredient, as a result of spontaneous chemical reaction(s), enzyme catalyzed chemical reaction(s), photolysis, and/or metabolic chemical reaction(s). A prodrug is thus a covalently modified analog or latent form of a therapeutically active compound.

[0030] One skilled in the art will recognize that substituents and other moieties of the compounds of Formula I should be selected in order to provide a compound which is sufficiently stable to provide a pharmaceutically useful compound which can be formulated into an acceptably stable pharmaceutical composition. Compounds of Formula I which have such stability are contemplated as falling within the scope of the present disclosure.

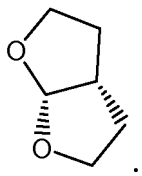
[0031] "Heteroalkyl" refers to an alkyl group where one or more carbon atoms have been replaced with a heteroatom, such as, O, N, or S. For example, if the carbon atom of the alkyl group which is attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkoxy group (e.g., $-OCH_3$, etc.), an amine (e.g., $-NHCH_3$, $-N(CH_3)_2$, etc.), or a thioalkyl group (e.g., $-SCH_3$). If a non-terminal carbon atom of the alkyl group which is not attached to the parent molecule is replaced with a heteroatom (e.g., O, N, or S) the resulting heteroalkyl groups are, respectively, an alkyl ether (e.g., $-CH_2CH_2$-O-CH_3, etc.), an alkyl amine (e.g., $-CH_2NHCH_3$, $-CH_2N(CH_3)_2$, etc.), or a thioalkyl ether (e.g.,$-CH_2$-S-CH_3). If a terminal carbon atom of the alkyl group is replaced with a heteroatom (e.g., O, N, or S), the resulting heteroalkyl groups are, respectively, a hydroxyalkyl group (e.g., $-CH_2CH_2$-OH), an aminoalkyl group (e.g., $-CH_2NH_2$), or an alkyl thiol group (e.g., $-CH_2CH_2$-SH). A heteroalkyl group can have, for example, 1 to 20 carbon atoms, 1 to 10 carbon atoms, or 1 to 6 carbon atoms. A C_1-C_6 heteroalkyl group means a heteroalkyl group having 1 to 6 carbon atoms.

[0032] "Heterocycle" or "heterocyclyl" as used herein includes by way of example and not limitation those heterocycles described in Paquette, Leo A.; Principles of Modern Heterocyclic Chemistry (W.A. Benjamin, New York, 1968), particularly Chapters 1, 3, 4, 6, 7, and 9; The Chemistry of Heterocyclic Compounds, A Series of Monographs" (John Wiley & Sons, New York, 1950 to present), in particular Volumes 13, 14, 16, 19, and 28; and J. Am. Chem. Soc. (1960) 82:5566. In one specific embodiment of the invention "heterocycle" includes a "carbocycle" as defined herein, wherein one or more

(*e.g.* 1, 2, 3, or 4) carbon atoms have been replaced with a heteroatom (*e.g.* O, N, or S). The terms "heterocycle" or "heterocyclyl" includes saturated rings, partially unsaturated rings, and aromatic rings (*i.e.,* heteroaromatic rings). Substituted heterocyclyls include, for example, heterocyclic rings substituted with any of the substituents disclosed herein including carbonyl groups. A non-limiting example of a carbonyl substituted heterocyclyl is:



[0033] Examples of heterocycles include by way of example and not limitation pyridyl, dihydroypyridyl, tetrahydropyridyl (piperidyl), thiazolyl, tetrahydrothiophenyl, sulfur oxidized tetrahydrothiophenyl, pyrimidinyl, furanyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, tetrazolyl, benzofuranyl, thianaphthalenyl, indolyl, indolenyl, quinolinyl, isoquinolinyl, benzimidazolyl, piperidinyl, 4-piperidonyl, pyrrolidinyl, 2-pyrrolidonyl, pyrrolinyl, tetrahydrofuranyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, decahydroquinolinyl, octahydroisoquinolinyl, azocinyl, triazinyl, 6H-1,2,5-thiadiazinyl, 2H,6H-1,5,2-dithiazinyl, thienyl, thianthrenyl, pyranyl, isobenzofuranyl, chromenyl, xanthenyl, phenoxathinyl, 2H-pyrrolyl, isothiazolyl, isoxazolyl, pyrazinyl, pyridazinyl, indolizinyl, isoindolyl, 3H-indolyl, 1H-indazoly, purinyl, 4H-quinolizinyl, phthalazinyl, naphthyridinyl, quinoxalinyl, quinazolinyl, cinnolinyl, pteridinyl, 4aH-carbazolyl, carbazolyl, β-carbolinyl, phenanthridinyl, acridinyl, pyrimidinyl, phenanthrolinyl, phenazinyl, phenothiazinyl, furazanyl, phenoxazinyl, isochromanyl, chromanyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, pyrazolinyl, piperazinyl, indolinyl, isoindolinyl, quinuclidinyl, morpholinyl, oxazolidinyl, benzotriazolyl, benzisoxazolyl, oxindolyl, benzoxazolinyl, isatinoyl, and bis-tetrahydrofuranyl:



[0034] By way of example and not limitation, carbon bonded heterocycles are bonded at position 2, 3, 4, 5, or 6 of a pyridine, position 3, 4, 5, or 6 of a pyridazine, position 2, 4, 5, or 6 of a pyrimidine, position 2, 3, 5, or 6 of a pyrazine, position 2, 3, 4, or 5 of a furan, tetrahydrofuran, thiofuran, thiophene, pyrrole or tetrahydropyrrole, position 2, 4, or 5 of an oxazole, imidazole or thiazole, position 3, 4, or 5 of an isoxazole, pyrazole, or isothiazole, position 2 or 3 of an aziridine, position 2, 3, or 4 of an azetidine, position 2, 3, 4, 5, 6, 7, or 8 of a quinoline or position 1, 3, 4, 5, 6, 7, or 8 of an isoquinoline. Still more typically, carbon bonded heterocycles include 2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl, 6-pyridyl, 3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl, 6-pyridazinyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl, 2-pyrazinyl, 3-pyrazinyl, 5-pyrazinyl, 6-pyrazinyl, 2-thiazolyl, 4-thiazolyl, or 5-thiazolyl.

[0035] By way of example and not limitation, nitrogen bonded heterocycles are bonded at position 1 of an aziridine, azetidine, pyrrole, pyrrolidine, 2-pyrroline, 3-pyrroline, imidazole, imidazolidine, 2-imidazoline, 3-imidazoline, pyrazole, pyrazoline, 2-pyrazoline, 3-pyrazoline, piperidine, piperazine, indole, indoline, 1H-indazole, position 2 of a isoindole, or isoindoline, position 4 of a morpholine, and position 9 of a carbazole, or β-carboline. Still more typically, nitrogen bonded heterocycles include 1-aziridyl, 1-azetedyl, 1-pyrrolyl, 1-imidazolyl, 1-pyrazolyl, and 1-piperidinyl.

[0036] "Heterocyclylalkyl" refers to an acyclic alkyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, is replaced with a heterocyclyl radical (*i.e.,* a heterocyclyl-alkylene- moiety). Typical heterocyclyl alkyl groups include, but are not limited to heterocyclyl-CH_2-, heterocyclyl-$CH(CH_3)$-, heterocyclyl-CH_2CH_2-, 2-(heterocyclyl)ethan-1-yl, and the like, wherein the "heterocyclyl" portion includes any of the heterocyclyl groups described above, including those described in Principles of Modern Heterocyclic Chemistry. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkyl portion of the heterocyclyl alkyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclylalkyl group comprises 2 to 20 carbon atoms, *e.g.*, the alkyl portion of the heterocyclylalkyl group is 1 to 6 carbon atoms and the heterocyclyl moiety is 1 to 14 carbon atoms. Examples of heterocyclylalkyls include by way of example and not limitation 5-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as thiazolylmethyl, 2-thiazolylethan-1-yl, imidazolylmethyl, oxazolylmethyl, thiadiazolylmethyl, etc., 6-membered sulfur, oxygen, and/or nitrogen containing heterocycles such as piperidinylmethyl, piperazinylmethyl, morpholinylmethyl, pyridinylmethyl, pyridizylmethyl, pyrimidylmethyl, pyrazinylmethyl, etc.

[0037] "Heterocyclylalkenyl" refers to an acyclic alkenyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also a sp^2 carbon atom, is replaced with a heterocyclyl radical (*i.e.,* a

heterocyclyl-alkenylene- moiety). The heterocyclyl portion of the heterocyclyl alkenyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkenyl portion of the heterocyclyl alkenyl group includes any of the alkenyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkenyl portion of the heterocyclyl alkenyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclylalkenyl group comprises 3 to 20 carbon atoms, *e.g.*, the alkenyl portion of the heterocyclyl alkenyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 1 to 14 carbon atoms.

[0038] "Heterocyclylalkynyl" refers to an acyclic alkynyl radical in which one of the hydrogen atoms bonded to a carbon atom, typically a terminal or sp^3 carbon atom, but also an sp carbon atom, is replaced with a heterocyclyl radical (*i.e.,* a heterocyclyl-alkynylene- moiety). The heterocyclyl portion of the heterocyclyl alkynyl group includes any of the heterocyclyl groups described herein, including those described in Principles of Modern Heterocyclic Chemistry, and the alkynyl portion of the heterocyclyl alkynyl group includes any of the alkynyl groups disclosed herein. One skilled in the art will also understand that the heterocyclyl group can be attached to the alkynyl portion of the heterocyclyl alkynyl by means of a carbon-carbon bond or a carbon-heteroatom bond, with the proviso that the resulting group is chemically stable. The heterocyclylalkynyl group comprises 3 to 20 carbon atoms, *e.g.*, the alkynyl portion of the heterocyclylalkynyl group is 2 to 6 carbon atoms and the heterocyclyl moiety is 1 to 14 carbon atoms.

[0039] "Heteroaryl" refers to an aromatic heterocyclyl having at least one heteroatom in the ring. Non-limiting examples of suitable heteroatoms which can be included in the aromatic ring include oxygen, sulfur, and nitrogen. Non-limiting examples of heteroaryl rings include all of those listed in the definition of "heterocyclyl", including pyridinyl, pyrrolyl, oxazolyl, indolyl, isoindolyl, purinyl, furanyl, thienyl, benzofuranyl, benzothiophenyl, carbazolyl, imidazolyl, thiazolyl, isoxazolyl, pyrazolyl, isothiazolyl, quinolyl, isoquinolyl, pyridazyl, pyrimidyl, pyrazyl, etc.

[0040] "Carbocycle" or "carbocyclyl" refers to a saturated (i.e., cycloalkyl), partially unsaturated (e.g., cycloakenyl, cycloalkadienyl, etc.) or aromatic ring having 3 to 7 carbon atoms as a monocycle, 7 to 12 carbon atoms as a bicycle, and up to about 20 carbon atoms as a polycycle. Monocyclic carbocycles have 3 to 6 ring atoms, still more typically 5 or 6 ring atoms. Bicyclic carbocycles have 7 to 12 ring atoms, *e.g.*, arranged as a bicyclo [4,5], [5,5], [5,6] or [6,6] system, or 9 or 10 ring atoms arranged as a bicyclo [5,6] or [6,6] system, or spiro-fused rings. Non-limiting examples of monocyclic carbocycles include cyclopropyl, cyclobutyl, cyclopentyl, 1-cyclopent-1-enyl, 1-cyclopent-2-enyl, 1-cyclopent-3-enyl, cyclohexyl, 1-cyclohex-1-enyl, 1-cyclohex-2-enyl, 1-cyclohex-3-enyl, and phenyl. Non-limiting examples of bicyclo carbocycles includes naphthyl.

[0041] "Arylheteroalkyl" refers to a heteroalkyl as defined herein, in which a hydrogen atom (which may be attached either to a carbon atom or a heteroatom) has been replaced with an aryl group as defined herein. The aryl groups may be bonded to a carbon atom of the heteroalkyl group, or to a heteroatom of the heteroalkyl group, provided that the resulting arylheteroalkyl group provides a chemically stable moiety. For example, an arylheteroalkyl group can have the general formulae -alkylene-O-aryl, -alkylene-O-alkylene-aryl, -alkylene-NH-aryl, -alkylene-NH-alkylene-aryl, -alkylene-S-aryl, -alkylene-S-alkylene-aryl, etc. In addition, any of the alkylene moieties in the general formulae above can be further substituted with any of the substituents defined or exemplified herein.

[0042] "Heteroarylalkyl" refers to an alkyl group, as defined herein, in which a hydrogen atom has been replaced with a heteroaryl group as defined herein. Non-limiting examples of heteroaryl alkyl include -CH_2-pyridinyl, -CH_2-pyrrolyl, -CH_2-oxazolyl, -CH_2-indolyl, -CH_2-isoindolyl, -CH_2-purinyl, -CH_2-furanyl, -CH_2-thienyl, -CH_2-benzofuranyl, -CH_2-benzothiophenyl, -CH_2-carbazolyl, -CH_2-imidazolyl, -CH_2-thiazolyl, -CH_2-isoxazolyl, -CH_2-pyrazolyl, -CH_2-isothiazolyl, -CH_2-quinolyl, -CH_2-isoquinolyl, -CH_2-pyridazyl, -CH_2-pyrimidyl, -CH_2-pyrazyl, -$CH(CH_3)$-pyridinyl, -$CH(CH_3)$-pyrrolyl, -$CH(CH_3)$-oxazolyl, -$CH(CH_3)$-indolyl, -$CH(CH_3)$-isoindolyl, -$CH(CH_3)$-purinyl, -$CH(CH_3)$-furanyl, -$CH(CH_3)$-thienyl, -$CH(CH_3)$-benzofuranyl, -$CH(CH_3)$-benzothiophenyl, -$CH(CH_3)$-carbazolyl, -$CH(CH_3)$-imidazolyl, -$CH(CH_3)$-thiazolyl, -$CH(CH_3)$-isoxazolyl, -$CH(CH_3)$-pyrazolyl, -$CH(CH_3)$-isothiazolyl, -$CH(CH_3)$-quinolyl, -$CH(CH_3)$-isoquinolyl, -$CH(CH_3)$-pyridazyl, -$CH(CH_3)$-pyrimidyl, -$CH(CH_3)$-pyrazyl, etc.

[0043] The term "optionally substituted" in reference to a particular moiety of the compound of Formula I (e.g., an optionally substituted aryl group) refers to a moiety having 0, 1, 2, or more substituents.

"Ac" means acetyl (-$C(O)CH_3$).
"Ac_2O" means acetic anhydride.
"DCM" means dichloromethane (CH_2Cl_2).
"DIBAL" means diisobutylaluminum hydride.
"DMAP" means dimethylaminopyridine.
"EDC" means 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide.
"Et" means ethyl.
"EtOAc" means ethylacetate.
"HOBt" means N-hydroxybenzotriazole.
"Me" means methyl (-CH_3).

"MeOH" means methanol.
"MeCN" means acetonitrile.
"Pr" means propyl.
"i-Pr" means isopropyl (-$CH(CH_3)_2$).
"i-PrOH" means isopropanol.
"rt" means room temperature.
"TFA" means trifluoroacetic acid.
"THF" means tetrahydrofuran.

[0044] The term "chiral" refers to molecules which have the property of non-superimposability of the mirror image partner, while the term "achiral" refers to molecules which are superimposable on their mirror image partner.

[0045] The term "stereoisomers" refers to compounds which have identical chemical constitution, but differ with regard to the arrangement of the atoms or groups in space.

[0046] "Diastereomer" refers to a stereoisomer with two or more centers of chirality and whose molecules are not mirror images of one another. Diastereomers have different physical properties, *e.g.*, melting points, boiling points, spectral properties, and reactivities. Mixtures of diastereomers may separate under high resolution analytical procedures such as electrophoresis and chromatography.

[0047] "Enantiomers" refer to two stereoisomers of a compound which are non-superimposable mirror images of one another.

[0048] Stereochemical definitions and conventions used herein generally follow S. P. Parker, Ed., McGraw-Hill Dictionary of Chemical Terms (1984) McGraw-Hill Book Company, New York; and Eliel, E. and Wilen, S., Stereochemistry of Organic Compounds (1994) John Wiley & Sons, Inc., New York. Many organic compounds exist in optically active forms, *i.e.,* they have the ability to rotate the plane of plane-polarized light. In describing an optically active compound, the prefixes D and L or R and S are used to denote the absolute configuration of the molecule about its chiral center(s). The prefixes d and 1 or (+) and (-) are employed to designate the sign of rotation of plane-polarized light by the compound, with (-) or 1 meaning that the compound is levorotatory. A compound prefixed with (+) or d is dextrorotatory. For a given chemical structure, these stereoisomers are identical except that they are mirror images of one another. A specific stereoisomer may also be referred to as an enantiomer, and a mixture of such isomers is often called an enantiomeric mixture. A 50:50 mixture of enantiomers is referred to as a racemic mixture or a racemate, which may occur where there has been no stereoselection or stereospecificity in a chemical reaction or process. The terms "racemic mixture" and "racemate" refer to an equimolar mixture of two enantiomeric species, devoid of optical activity.

Protecting Groups

[0049] In the context of the present disclosure, protecting groups include prodrug moieties and chemical protecting groups.

[0050] Protecting groups are available, commonly known and used, and are optionally used to prevent side reactions with the protected group during synthetic procedures, *i.e*. routes or methods to prepare the compounds of the invention. For the most part the decision as to which groups to protect, when to do so, and the nature of the chemical protecting group "PG" will be dependent upon the chemistry of the reaction to be protected against (*e.g.,* acidic, basic, oxidative, reductive or other conditions) and the intended direction of the synthesis. The PG groups do not need to be, and generally are not, the same if the compound is substituted with multiple PG. In general, PG will be used to protect functional groups such as carboxyl, hydroxyl, thio, or amino groups and to thus prevent side reactions or to otherwise facilitate the synthetic efficiency. The order of deprotection to yield free, deprotected groups is dependent upon the intended direction of the synthesis and the reaction conditions to be encountered, and may occur in any order as determined by the artisan.

[0051] Various functional groups of the compounds of the invention may be protected. For example, protecting groups for -OH groups (whether hydroxyl, carboxylic acid, phosphonic acid, or other functions) include "ether- or ester-forming groups". Ether- or ester-forming groups are capable of functioning as chemical protecting groups in the synthetic schemes set forth herein. However, some hydroxyl and thio protecting groups are neither ether- nor ester-forming groups, as will be understood by those skilled in the art, and are included with amides, discussed below.

[0052] A very large number of hydroxyl protecting groups and amide-forming groups and corresponding chemical cleavage reactions are described in Protective Groups in Organic Synthesis, Theodora W. Greene and Peter G. M. Wuts (John Wiley & Sons, Inc., New York, 1999, ISBN 0-471-16019-9) ("Greene"). See also Kocienski, Philip J.; Protecting Groups (Georg Thieme Verlag Stuttgart, New York, 1994). In particular Chapter 1, Protecting Groups: An Overview, pages 1-20, Chapter 2, Hydroxyl Protecting Groups, pages 21-94, Chapter 3, Diol Protecting Groups, pages 95-117, Chapter 4, Carboxyl Protecting Groups, pages 118-154, Chapter 5, Carbonyl Protecting Groups, pages 155-184. For protecting groups for carboxylic acid, phosphonic acid, phosphonate, sulfonic acid and other protecting groups for acids see Greene as set forth below. Such groups include by way of example and not limitation, esters, amides, hydrazides,

and the like.

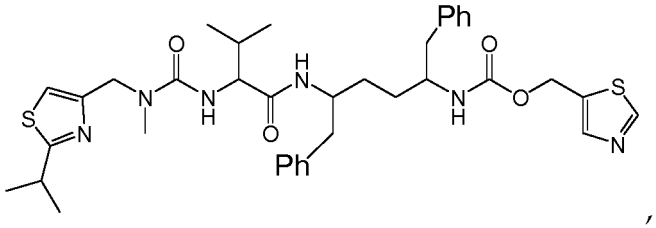
Ether- and Ester-forming protecting groups

[0053] Ester-forming groups include: (1) phosphonate ester-forming groups, such as phosphonamidate esters, phosphorothioate esters, phosphonate esters, and phosphon-bis-amidates; (2) carboxyl ester-forming groups, and (3) sulphur ester-forming groups, such as sulphonate, sulfate, and sulfinate.

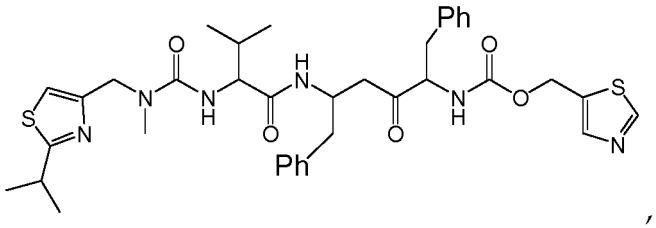
Metabolites of the Compounds of the Invention

[0054] Also falling within the scope of this disclosure are the in vivo metabolic products of the compounds described herein. Such products may result for example from the oxidation, reduction, hydrolysis, amidation, esterification and the like of the administered compound, primarily due to enzymatic processes. Accordingly, the disclosure includes compounds produced by a process comprising contacting a compound of this invention with a mammal for a period of time sufficient to yield a metabolic product thereof. Such products typically are identified by preparing a radiolabelled (e.g., C^{14} or H^3) compound of the invention, administering it parenterally in a detectable dose (e.g., greater than about 0.5 mg/kg) to an animal such as rat, mouse, guinea pig, monkey, or to man, allowing sufficient time for metabolism to occur (typically about 30 seconds to 30 hours) and isolating its conversion products from the urine, blood or other biological samples. These products are easily isolated since they are labeled (others are isolated by the use of antibodies capable of binding epitopes surviving in the metabolite). The metabolite structures are determined in conventional fashion, e.g., by MS or NMR analysis. In general, analysis of metabolites is done in the same way as conventional drug metabolism studies well-known to those skilled in the art. The conversion products, so long as they are not otherwise found in vivo, are useful in diagnostic assays for therapeutic dosing of the compounds of the invention even if they possess no anti-infective activity of their own.

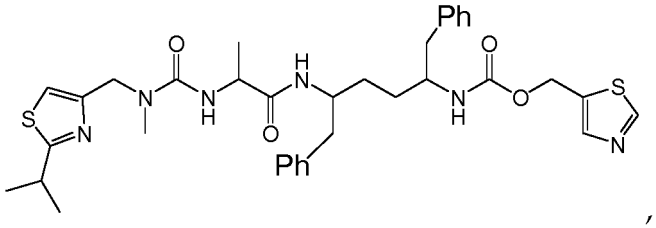
[0055] Compounds of Formula I may have one of the following structures:



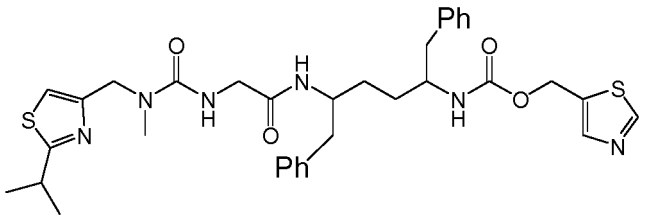
,



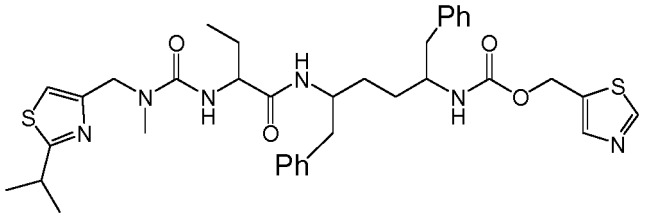
,



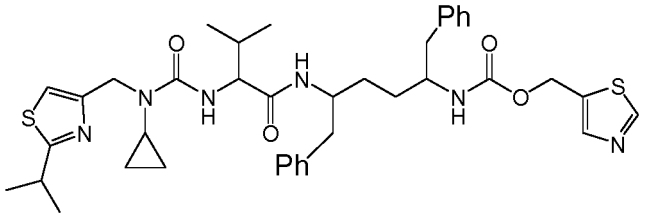
,



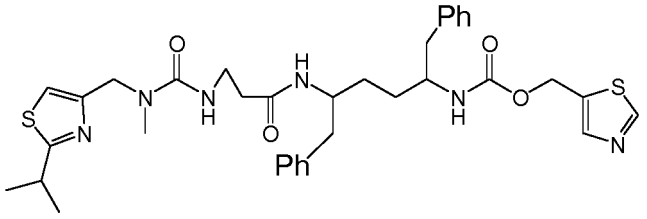
,



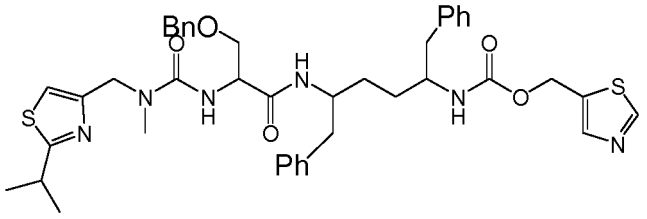
,



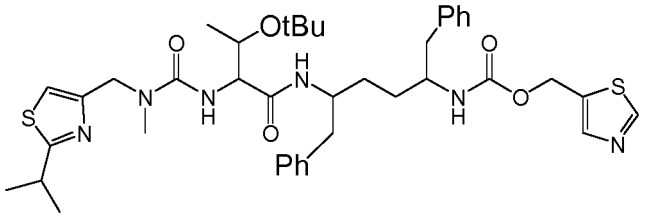
,



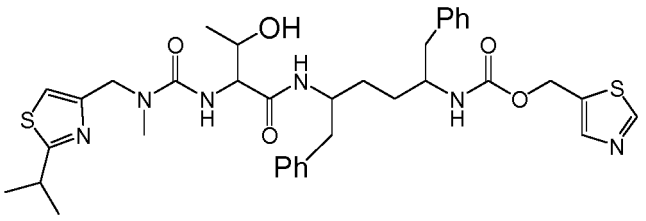
,



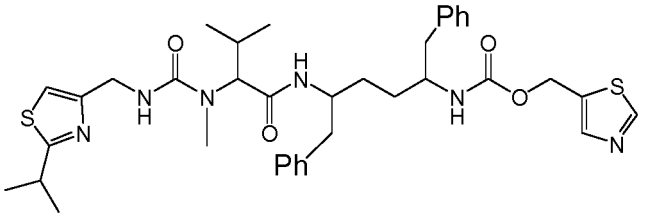
,



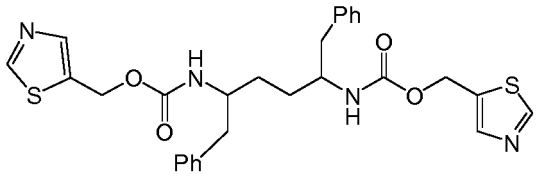
,



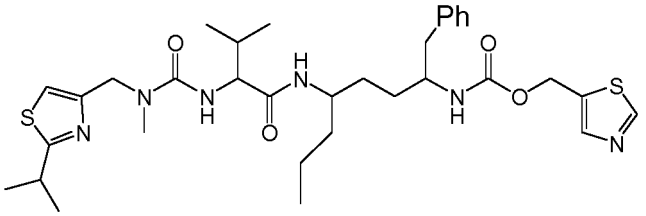
,



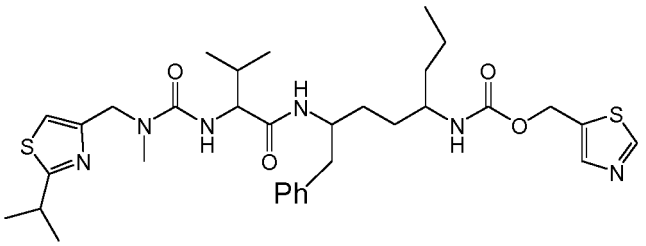
,



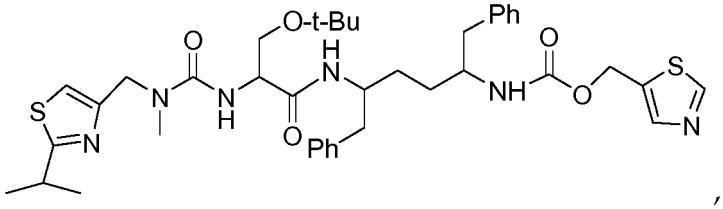
,



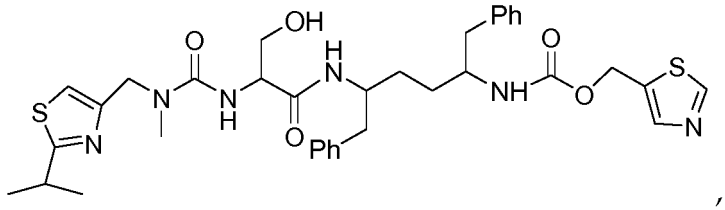
,



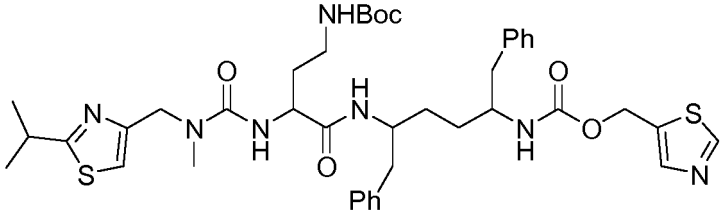
,



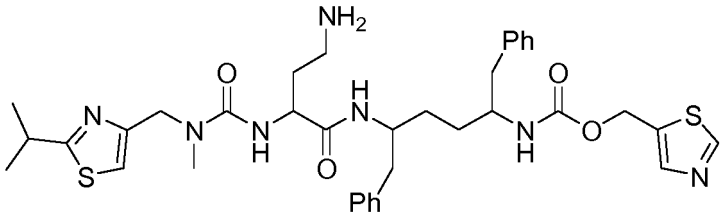
,



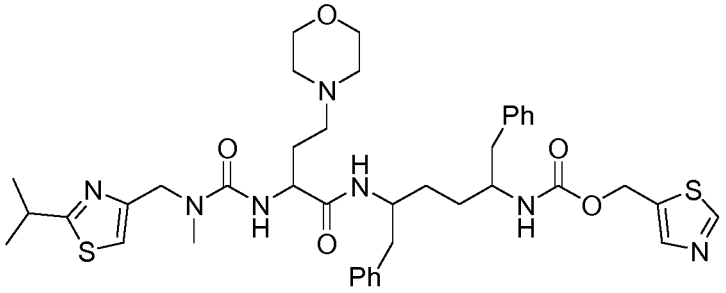
,



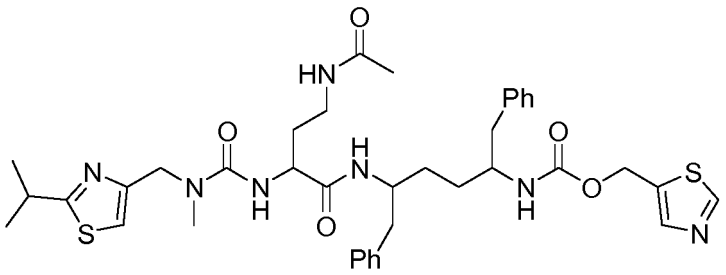
,



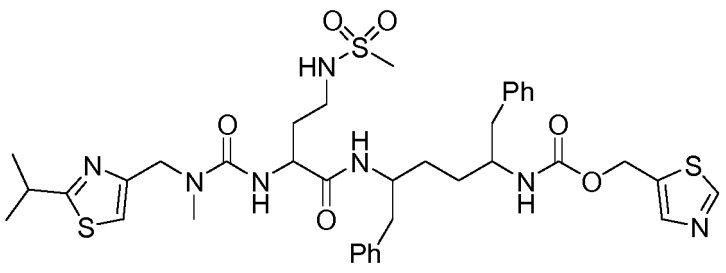
,



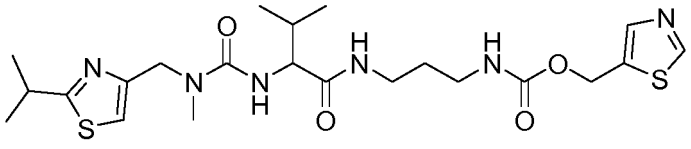
,



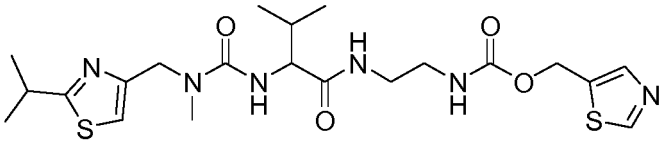
,



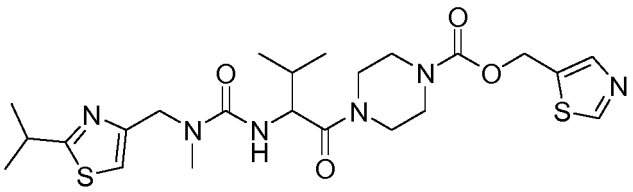
,



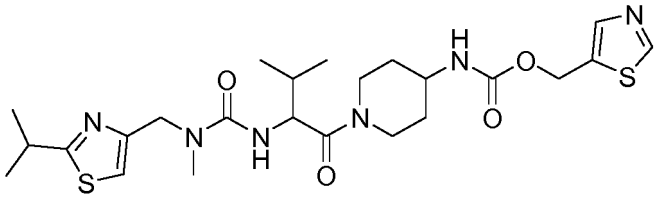
,



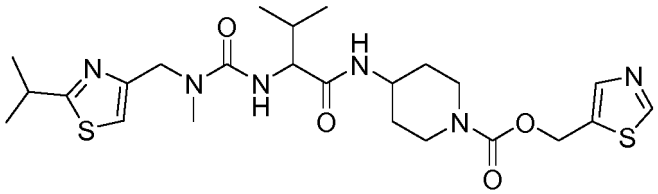
,



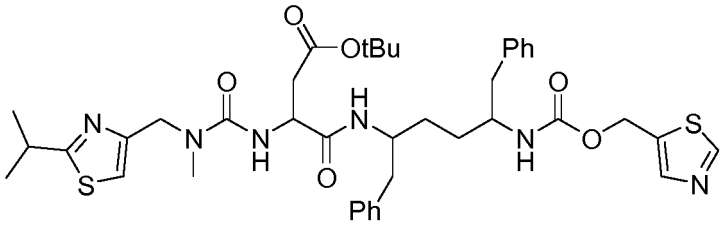
,



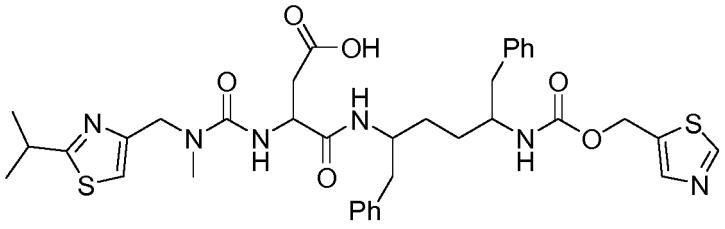
,



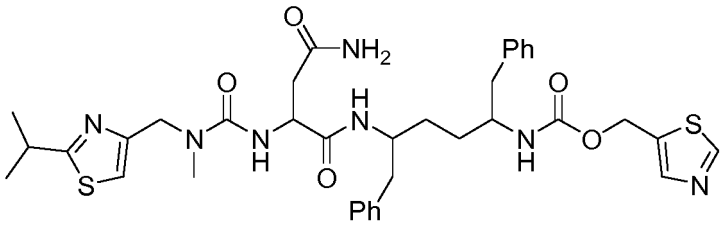
,



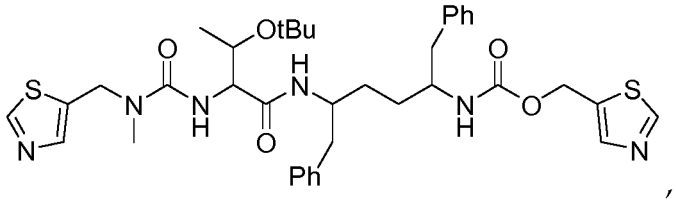
,



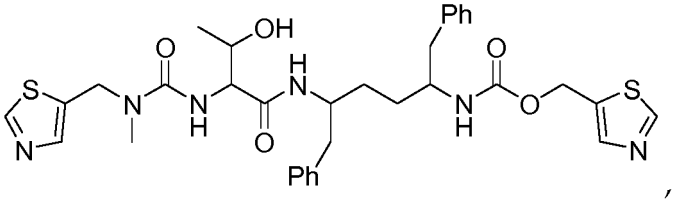
,



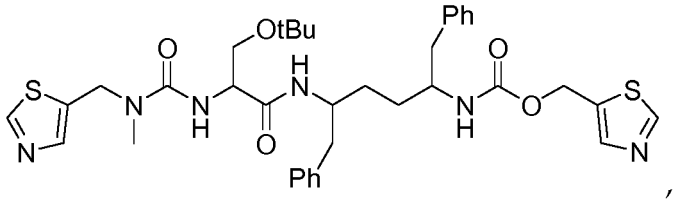
,



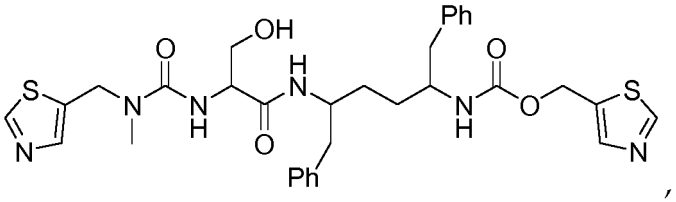
,



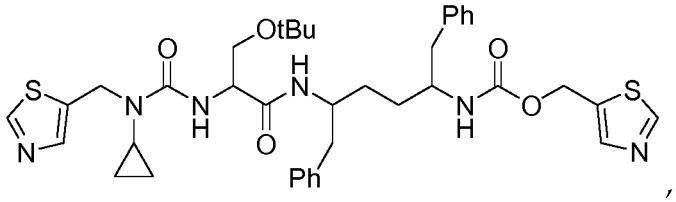
,



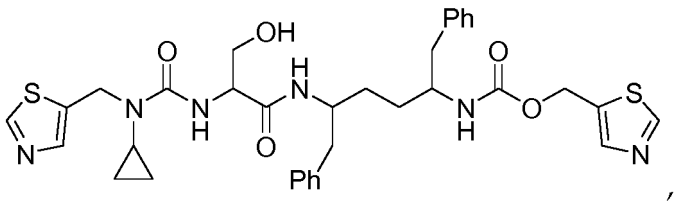
,



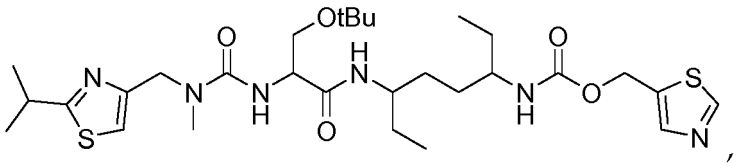
,



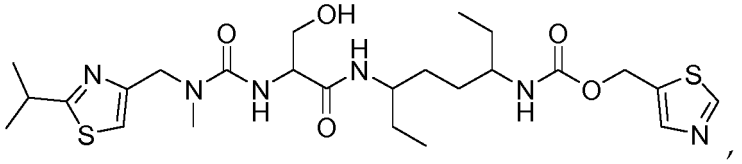
,



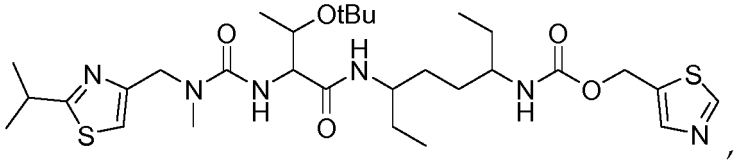
,



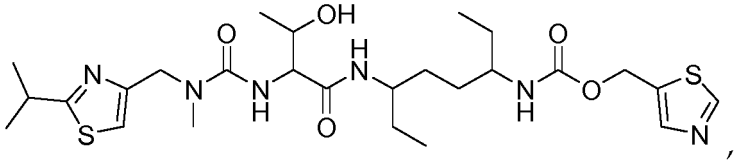
,



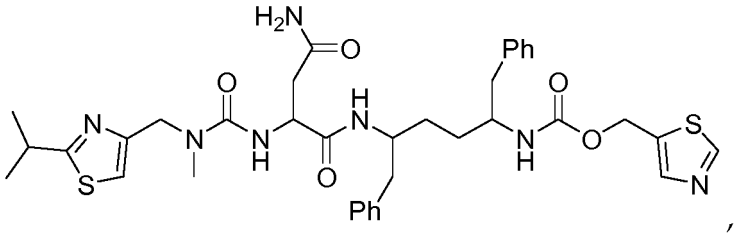
,



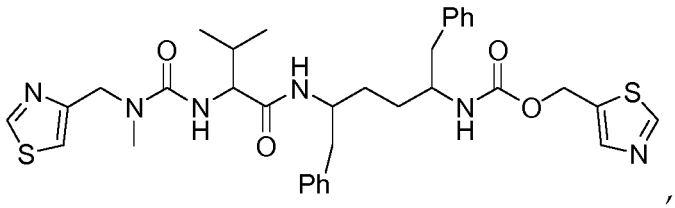
,



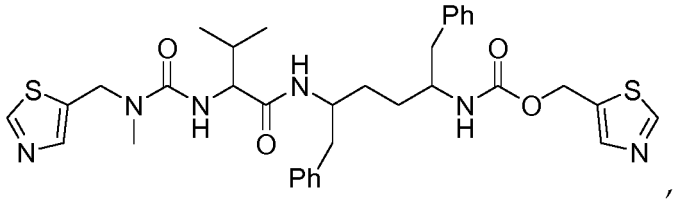
,



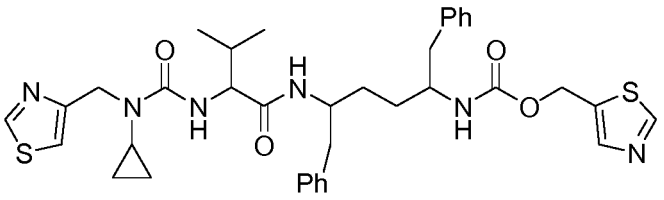
,



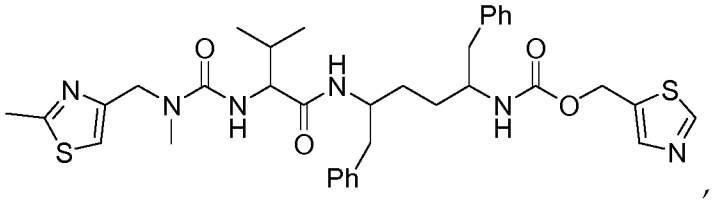
,



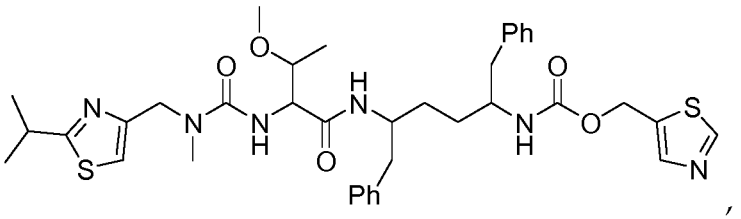
,



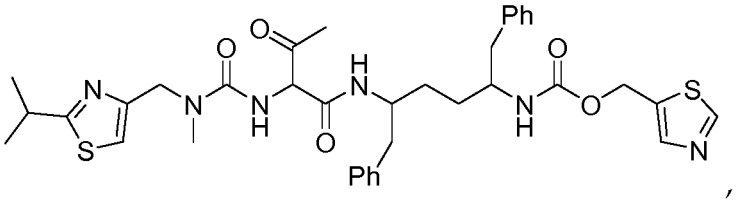
,



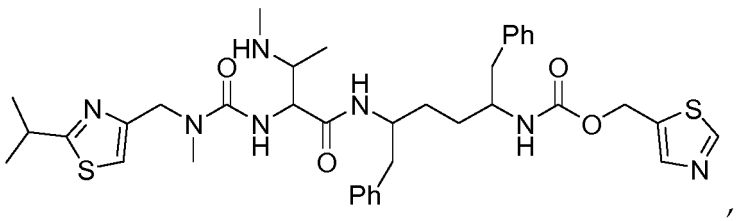
,



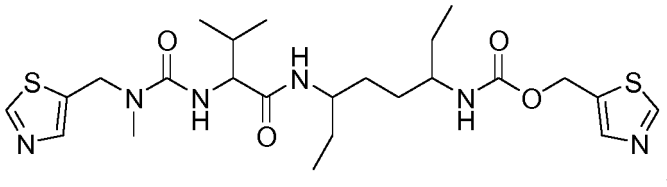
,



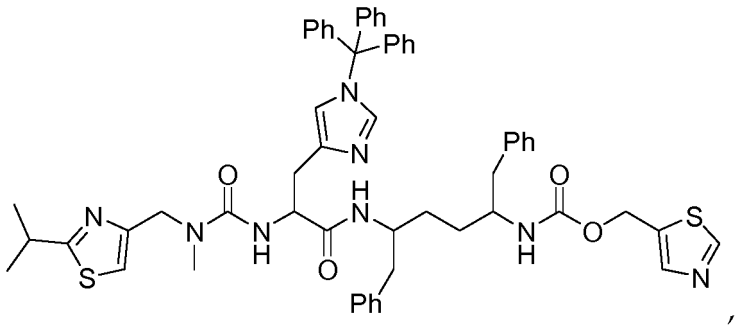
,



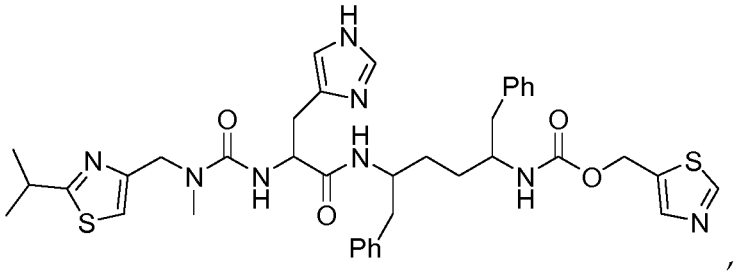
,



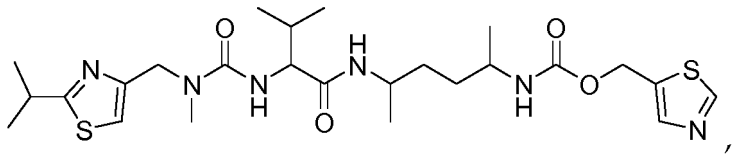
,



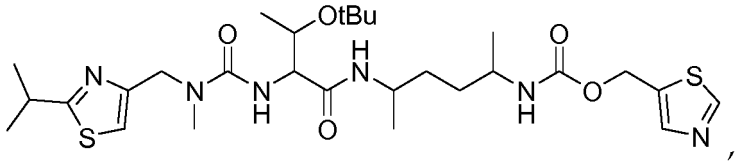
,



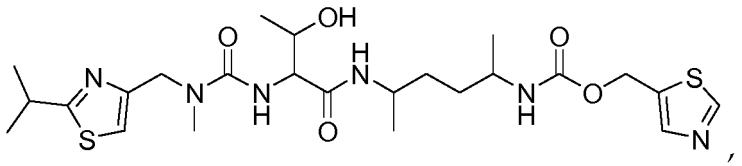
,



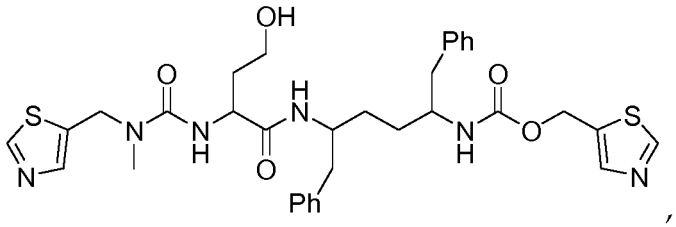
,



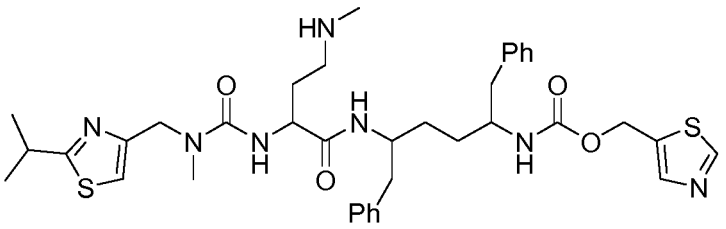
,



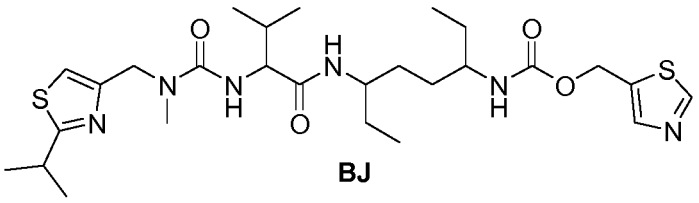
,



,

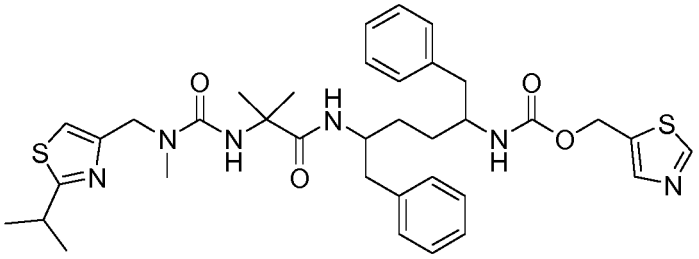


,

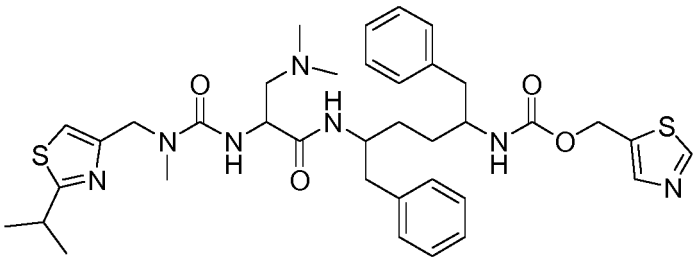


BJ

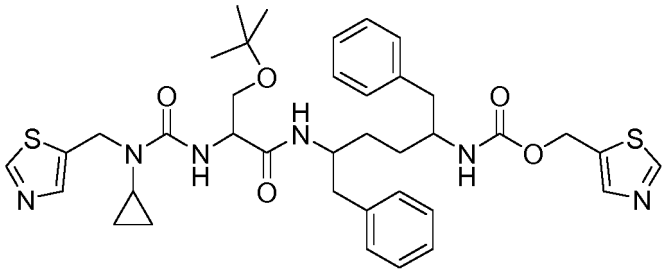
,



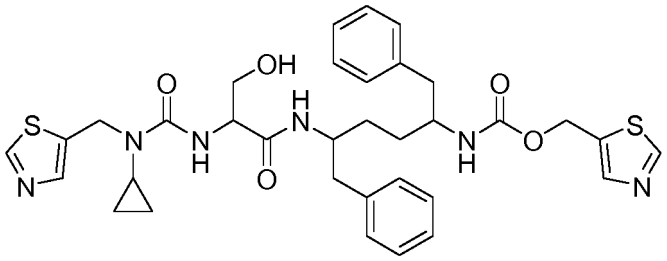
,



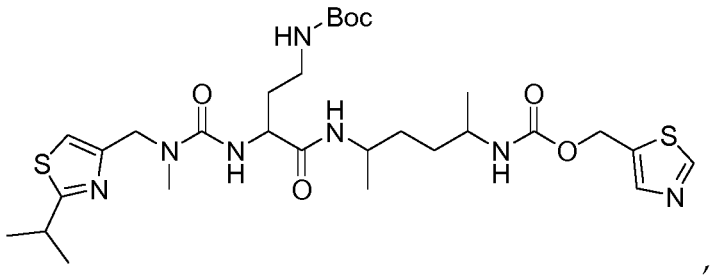
,



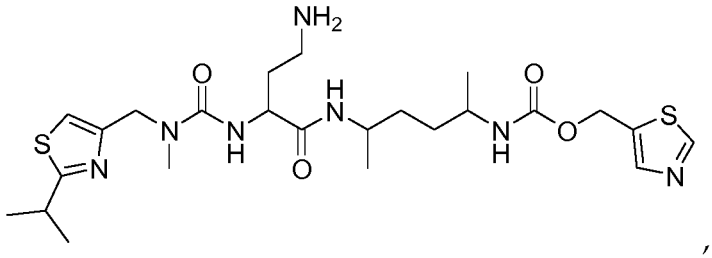
,



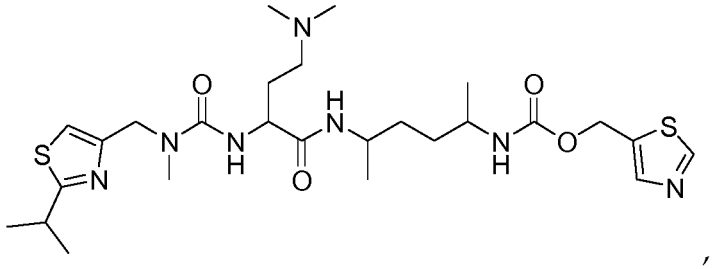
,



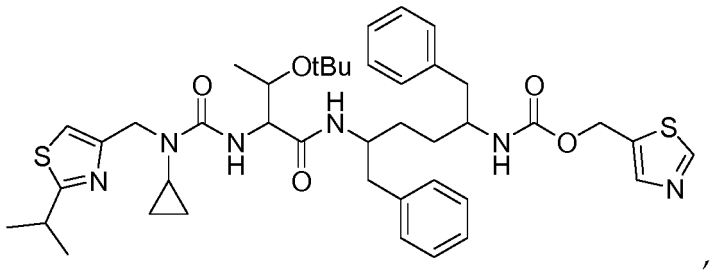
,



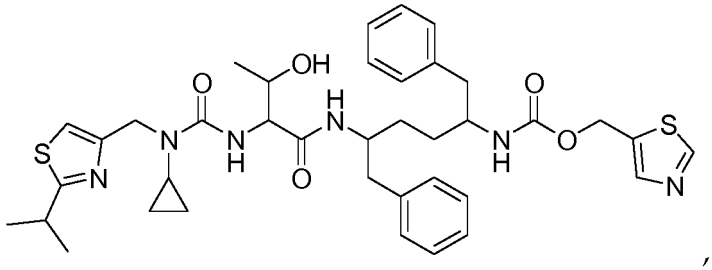
,



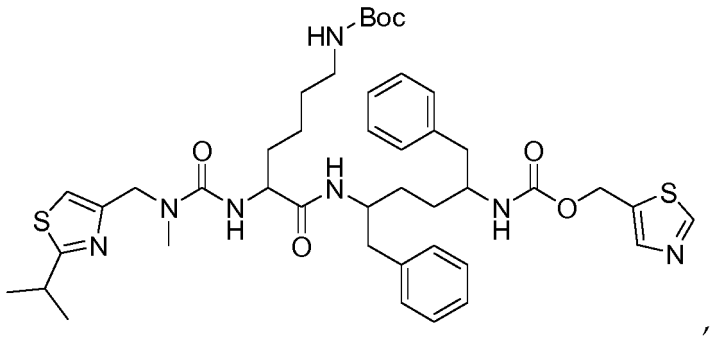
,



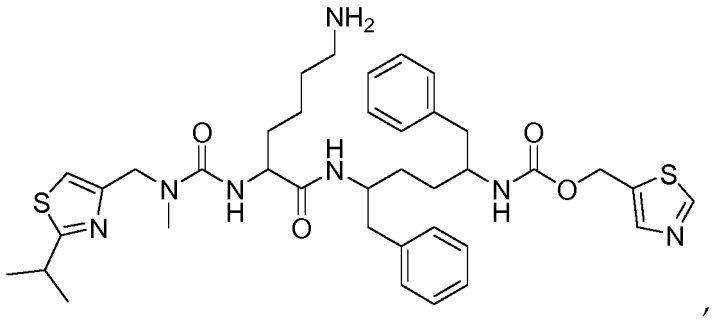
,



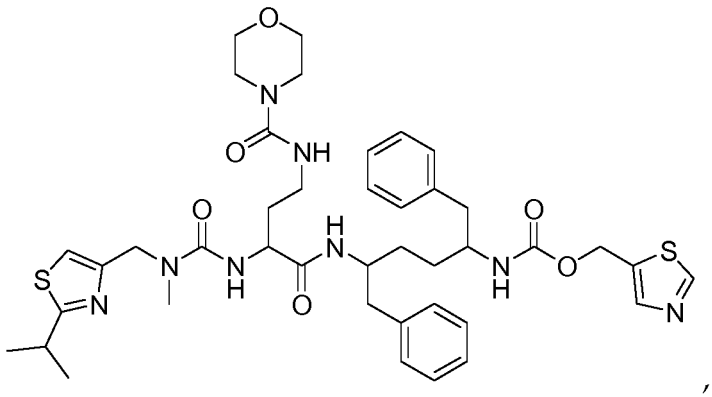
,


HN
Boc
O
H
N
O
N
H
N
O
O
S
N
S
N

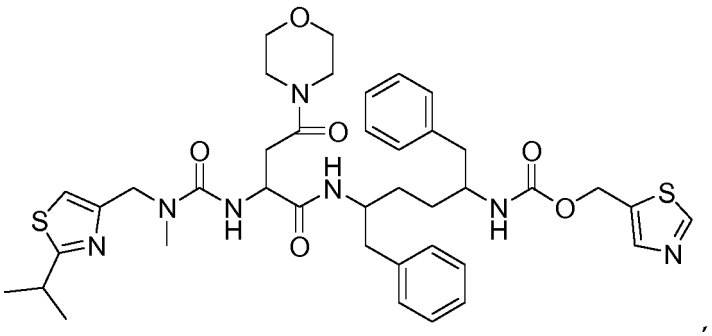
,


NH2
O
H
N
O
N
H
N
O
O
S
N
S
N

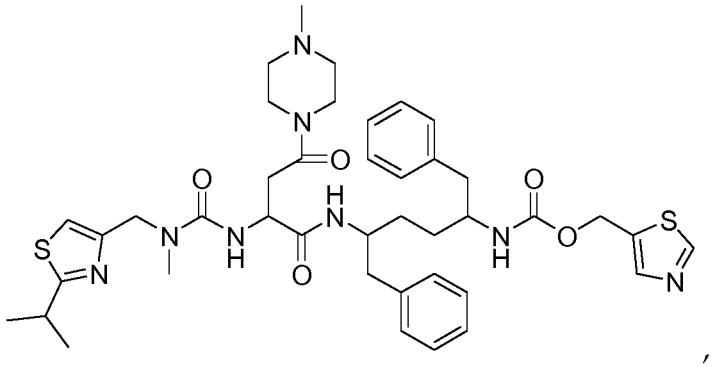
,


O
N
O
NH
O
H
N
O
N
H
N
O
O
S
N
S
N

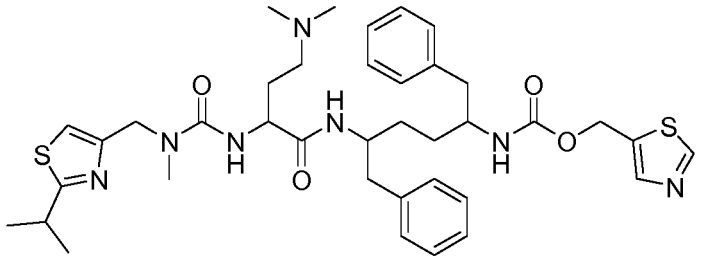
,


O
N
O
O
H
N
O
N
H
N
O
O
S
N
S
N

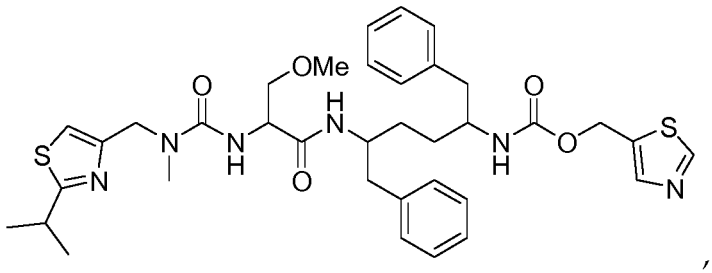
,



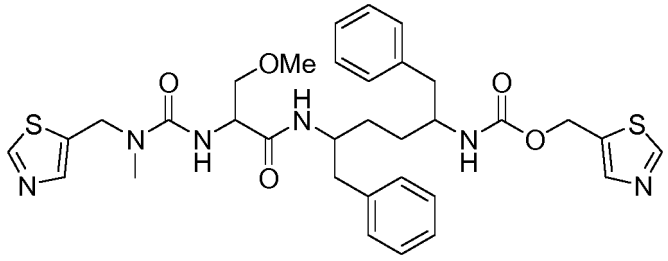
,



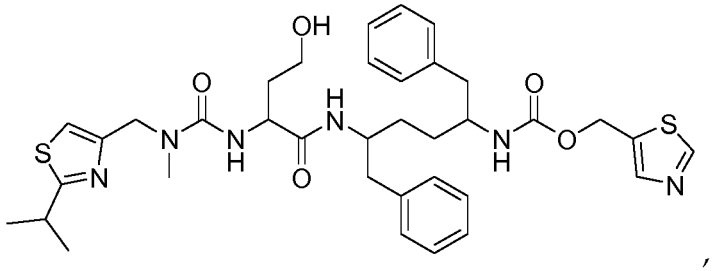
,



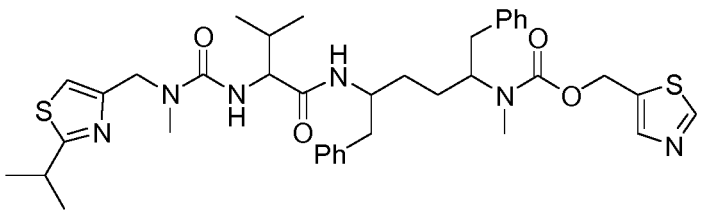
,



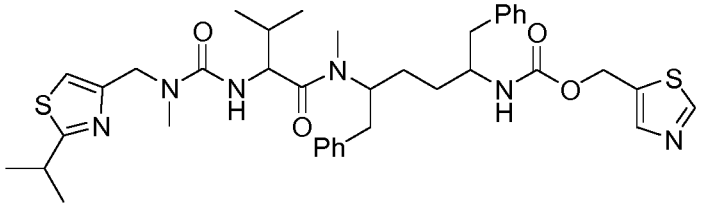
,



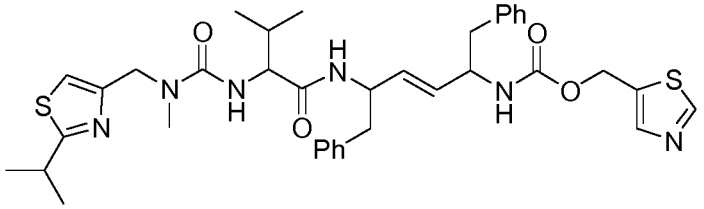
,



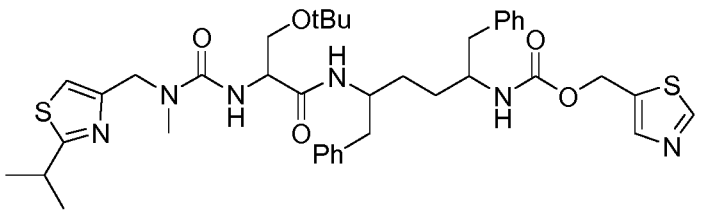
,



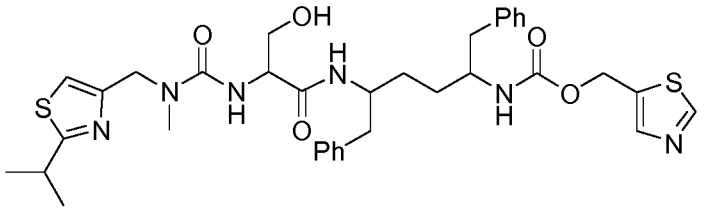
,



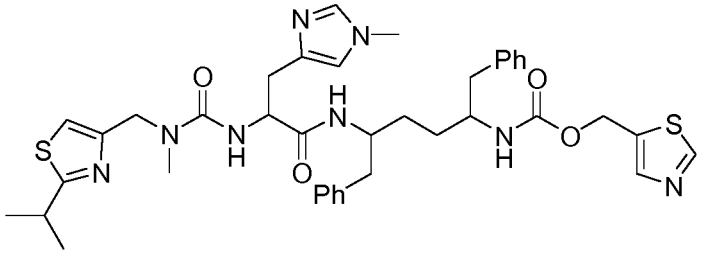
,



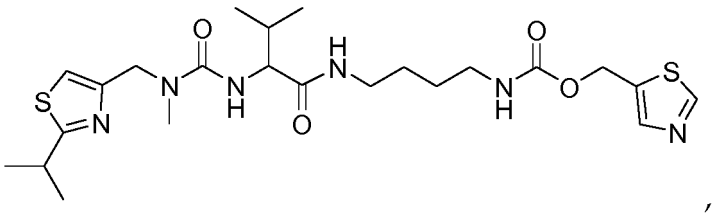
,



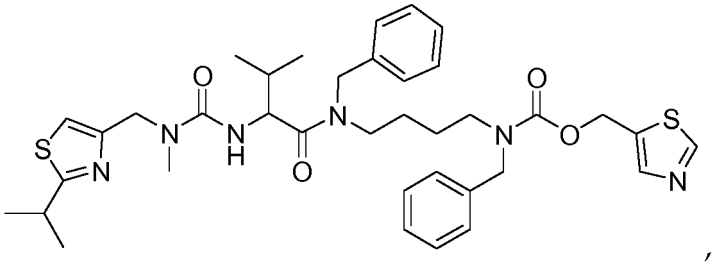
,



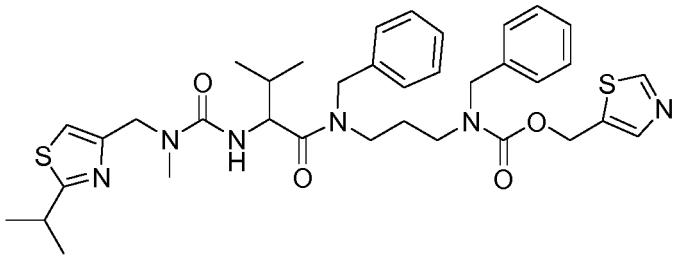
,



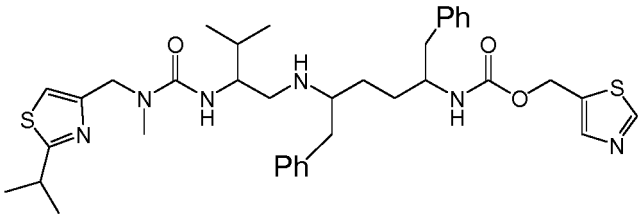
,



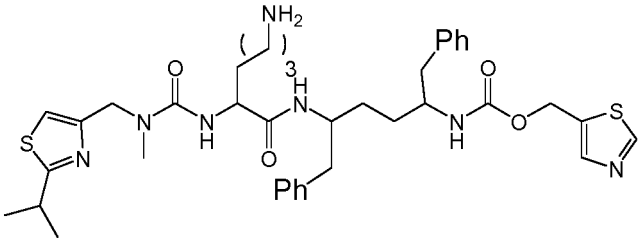
,



,

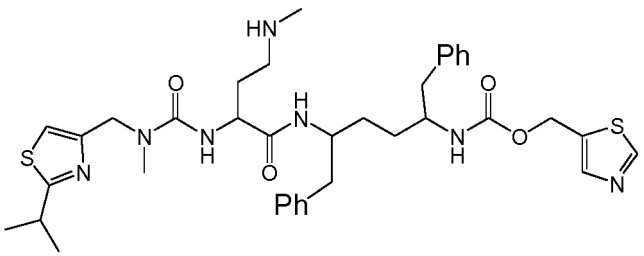


,



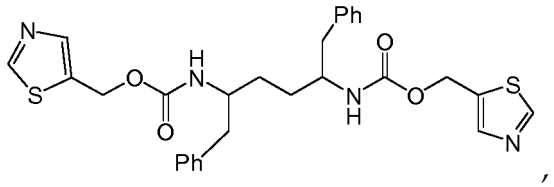
,

and

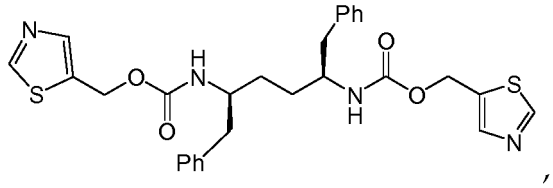


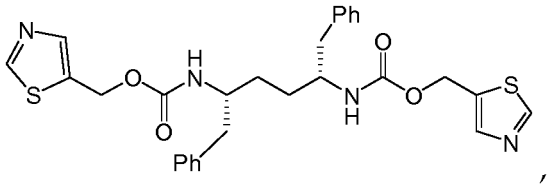
;

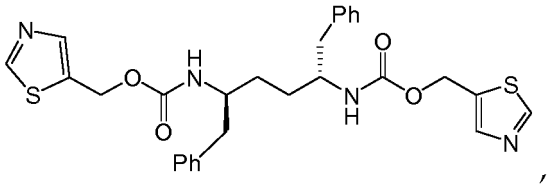
including stereoisomers or mixtures of stereoisomers thereof. One skilled in the art will recognize that stereoisomers or mixtures of stereoisomers of the compounds of the present application include enantiomers, diastereomers, and other stereoisomers. For example, for:



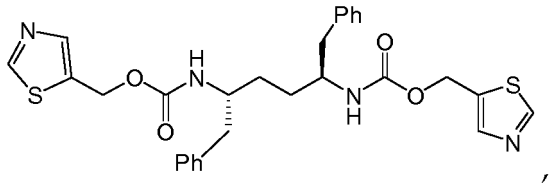
contemplated stereoisomers include at least:







and



as well as mixtures of two or more of these stereoisomers.

[0056] In still yet another embodiment, the compound of the present invention has an inhibition activity against P450 at a level equal to or better than the inhibition activity of a compound as represented by an IC_{50} of less than about 2000 nM, less than about 1500 nM, less than about 1000 nM, less than about 900 nM, less than about 800 nM, less than about 700 nM, less than about 650 nM, less than about 600 nM, less than about 550 nM, less than about 500 nM, less than about 400 nM, less than about 350 nM, less than about 300 nM, less than about 250 nM, less than about 200 nM, less than about 100 nM, or less than about 50 nM.

[0057] In still yet another embodiment, the compound of the present invention has an inhibition activity against an isozyme of P450, *e.g.*, 3A in a range represented by IC_{50} from about 2000 nM to about 100 nM, from about 1000 nM to about 100 nM, from about 900 nM to about 200 nM, from about 800 nM to about 300 nM, from about 700 nM to about 200 nM, from about 600 nM to about 200 nM, from about 500 nM to about 200 nM, from about 700 nM to about 300 nM, from about 600 nM to about 300 nM, from about 700 nM to about 400 nM, from about 600 nM to about 400 nM, from about 400 nM to about 100 nM, from about 300 nM to about 100 nM, or from about 600 nM to about 150 nM.

[0058] In still yet another embodiment, the compound of the present invention has an inhibition activity against P450 at a level equal to or better than the inhibition activity of a compound as represented by an IC_{50} of less than about 2000 nM, less than about 1500 nM, less than about 1000 nM, less than about 900 nM, less than about 800 nM, less than about 700 nM, less than about 650 nM, less than about 600 nM, less than about 550 nM, less than about 500 nM, less than about 400 nM, less than about 350 nM, less than about 300 nM, less than about 250 nM, less than about 200 nM, less than about 100 nM, or less than about 50 nM, provided that such compound also does not substantially exhibit biological activities other than its inhibition activity against P450. For example, the compound of the present invention

can have a reduced or not significant activity of protease inhibition, including without any limitation a level of protease inhibition as represented by HIV EC_{50} of greater than about 1000 nM, greater than about 900 nM, greater than about 800 nM, greater than about 700 nM, greater than about 600 nM, greater than about 500 nM, greater than about 400 nM, greater than about 300 nM, greater than about 200 nM, greater than about 100 nM, greater than about 50 nM, greater than about 40 nM, greater than about 30 nM, greater than about 20 nM, greater than about 10 nM, greater than about 5 nM, or greater than about 1 nM.

[0059] In yet another embodiment, the compound of the present invention has an inhibition activity specifically against one or more isozymes of P450 including without limitation 1A2, 2B6, 2C8, 2C19, 2C9, 2D6, 2E1, and 3A4, 5, 7, etc.

[0060] In yet another embodiment, the compound of the present invention has an inhibition activity specifically against an isozyme of P450 that is involved in metabolizing anti-viral drugs, *e.g.*, indinavir, nelfinavir, ritonavir, saquinavir etc.

[0061] In still yet another embodiment, the compound of the present invention has an inhibition activity specifically against one or more isozymes of P450, but not the other(s). For example, the compound of the present invention can have an inhibition activity specifically against P450 3A, but a reduced, insubstantial, or minimum inhibition activity against another isozyme of P450, *e.g.*, P450 2C9.

Pharmaceutical Formulations

[0062] The compounds of this invention are formulated with conventional carriers and excipients, which will be selected in accord with ordinary practice. Tablets will contain excipients, glidants, fillers, binders and the like. Aqueous formulations are prepared in sterile form, and when intended for delivery by other than oral administration generally will be isotonic. All formulations will optionally contain excipients such as those set forth in the Handbook of Pharmaceutical Excipients (1986). Excipients include ascorbic acid and other antioxidants, chelating agents such as EDTA, carbohydrates such as dextrin, hydroxyalkylcellulose, hydroxyalkylmethylcellulose, stearic acid and the like. The pH of the formulations ranges from about 3 to about 11, but is ordinarily about 7 to 10.

[0063] While it is possible for the active ingredients to be administered alone it may be preferable to present them as pharmaceutical formulations. The formulations of the invention, both for veterinary and for human use, comprise at least one active ingredient, e.g. a compound of the present invention, together with one or more acceptable carriers and optionally other therapeutic ingredients. The carrier(s) must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and physiologically innocuous to the recipient thereof.

[0064] The formulations include those suitable for the foregoing administration routes. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. Techniques and formulations generally are found in Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.). Such methods include the step of bringing into association the active ingredient with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both, and then, if necessary, shaping the product.

[0065] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous or non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be administered as a bolus, electuary or paste.

[0066] A tablet is made by compression or molding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, preservative, surface active or dispersing agent. Molded tablets may be made by molding in a suitable machine a mixture of the powdered active ingredient moistened with an inert liquid diluent. The tablets may optionally be coated or scored and optionally are formulated so as to provide slow or controlled release of the active ingredient.

[0067] For administration to the eye or other external tissues e.g., mouth and skin, the formulations are preferably applied as a topical ointment or cream containing the active ingredient(s) in an amount of, for example, 0.075 to 20% w/w (including active ingredient(s) in a range between 0.1% and 20% in increments of 0.1% w/w such as 0.6% w/w, 0.7% w/w, etc.), preferably 0.2 to 15% w/w and most preferably 0.5 to 10% w/w. When formulated in an ointment, the active ingredients may be employed with either a paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base.

[0068] If desired, the aqueous phase of the cream base may include, for example, at least 30% w/w of a polyhydric alcohol, *i.e.* an alcohol having two or more hydroxyl groups such as propylene glycol, butane 1,3-diol, mannitol, sorbitol, glycerol and polyethylene glycol (including PEG 400) and mixtures thereof. The topical formulations may desirably include a compound which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include dimethyl sulphoxide and related analogs.

[0069] The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner.

While the phase may comprise merely an emulsifier (otherwise known as an emulgent), it desirably comprises a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base which forms the oily dispersed phase of the cream formulations.

[0070] Emulgents and emulsion stabilizers suitable for use in the formulation of the invention include Tween® 60, Span® 80, cetostearyl alcohol, benzyl alcohol, myristyl alcohol, glyceryl mono-stearate and sodium lauryl sulfate.

[0071] The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties. The cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters known as Crodamol CAP may be used, the last three being preferred esters. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils are used.

[0072] Pharmaceutical formulations according to the present invention comprise one or more compounds of the invention together with one or more pharmaceutically acceptable carriers or excipients and optionally other therapeutic agents. Pharmaceutical formulations containing the active ingredient may be in any form suitable for the intended method of administration. When used for oral use for example, tablets, troches, lozenges, aqueous or oil suspensions, dispersible powders or granules, emulsions, hard or soft capsules, syrups or elixirs may be prepared. Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents including sweetening agents, flavoring agents, coloring agents and preserving agents, in order to provide a palatable preparation. Tablets containing the active ingredient in admixture with non-toxic pharmaceutically acceptable excipient which are suitable for manufacture of tablets are acceptable. These excipients may be, for example, inert diluents, such as calcium or sodium carbonate, lactose, lactose monohydrate, croscarmellose sodium, povidone, calcium or sodium phosphate; granulating and disintegrating agents, such as maize starch, or alginic acid; binding agents, such as cellulose, microcrystalline cellulose, starch, gelatin or acacia; and lubricating agents, such as magnesium stearate, stearic acid or talc. Tablets may be uncoated or may be coated by known techniques including microencapsulation to delay disintegration and adsorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate alone or with a wax may be employed.

[0073] Formulations for oral use may be also presented as hard gelatin capsules where the active ingredient is mixed with an inert solid diluent, for example calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, such as peanut oil, liquid paraffin or olive oil.

[0074] Aqueous suspensions of the invention contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients include a suspending agent, such as sodium carboxymethylcellulose, methylcellulose, hydroxypropyl methylcelluose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia, and dispersing or wetting agents such as a naturally occurring phosphatide (e.g., lecithin), a condensation product of an alkylene oxide with a fatty acid (e.g., polyoxyethylene stearate), a condensation product of ethylene oxide with a long chain aliphatic alcohol (e.g., heptadecaethyleneoxycetanol), a condensation product of ethylene oxide with a partial ester derived from a fatty acid and a hexitol anhydride (e.g., polyoxyethylene sorbitan monooleate). The aqueous suspension may also contain one or more preservatives such as ethyl or n-propyl p-hydroxy-benzoate, one or more coloring agents, one or more flavoring agents and one or more sweetening agents, such as sucrose or saccharin.

[0075] Oil suspensions may be formulated by suspending the active ingredient in a vegetable oil, such as arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oral suspensions may contain a thickening agent, such as beeswax, hard paraffin or cetyl alcohol. Sweetening agents, such as those set forth herein, and flavoring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an antioxidant such as ascorbic acid.

[0076] Dispersible powders and granules of the invention suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, a suspending agent, and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those disclosed above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

[0077] The pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, such as olive oil or arachis oil, a mineral oil, such as liquid paraffin, or a mixture of these. Suitable emulsifying agents include naturally-occurring gums, such as gum acacia and gum tragacanth, naturally occurring phosphatides, such as soybean lecithin, esters or partial esters derived from fatty acids and hexitol anhydrides, such as sorbitan monooleate, and condensation products of these partial esters with ethylene oxide, such as polyoxyethylene sorbitan monooleate. The emulsion may also contain sweetening and flavoring agents. Syrups and elixirs may be formulated with sweetening agents, such as glycerol, sorbitol or sucrose. Such formulations may also contain

a demulcent, a preservative, a flavoring or a coloring agent.

[0078] The pharmaceutical compositions of the invention may be in the form of a sterile injectable preparation, such as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned herein. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally acceptable diluent or solvent, such as a solution in 1,3-butane-diol or prepared as a lyophilized powder. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile fixed oils may conventionally be employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid may likewise be used in the preparation of injectables.

[0079] The amount of active ingredient that may be combined with the carrier material to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. For example, a time-release formulation intended for oral administration to humans may contain approximately 1 to 1000 mg of active material compounded with an appropriate and convenient amount of carrier material which may vary from about 5 to about 95% of the total compositions (weight:weight). The pharmaceutical composition can be prepared to provide easily measurable amounts for administration. For example, an aqueous solution intended for intravenous infusion may contain from about 3 to 500 μg of the active ingredient per milliliter of solution in order that infusion of a suitable volume at a rate of about 30 mL/hr can occur.

[0080] Formulations suitable for administration to the eye include eye drops wherein the active ingredient is dissolved or suspended in a suitable carrier, especially an aqueous solvent for the active ingredient. The active ingredient is preferably present in such formulations in a concentration of 0.5 to 20%, advantageously 0.5 to 10% particularly about 1.5% w/w.

[0081] Formulations suitable for topical administration in the mouth include lozenges comprising the active ingredient in a flavored basis, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert basis such as gelatin and glycerin, or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

[0082] Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

[0083] Formulations suitable for intrapulmonary or nasal administration have a particle size for example in the range of 0.1 to 500 μm (including particle sizes in a range between 0.1 and 500 μm in increments such as 0.5 μm, 1 μm, 30 μm, 35 μm, etc.), which is administered by rapid inhalation through the nasal passage or by inhalation through the mouth so as to reach the alveolar sacs. Suitable formulations include aqueous or oily solutions of the active ingredient. Formulations suitable for aerosol or dry powder administration may be prepared according to conventional methods and may be delivered with other therapeutic agents such as compounds heretofore used in the treatment or prophylaxis of infections as described herein.

[0084] Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

[0085] Formulations suitable for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents.

[0086] The formulations are presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilized) condition requiring only the addition of the sterile liquid carrier, for example water for injection, immediately prior to use. Extemporaneous injection solutions and suspensions are prepared from sterile powders, granules and tablets of the kind previously described. Preferred unit dosage formulations are those containing a daily dose or unit daily sub-dose, as herein above recited, or an appropriate fraction thereof, of the active ingredient.

[0087] It should be understood that in addition to the ingredients provided by the present invention the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring agents.

[0088] The invention further provides veterinary compositions comprising at least one active ingredient, *e.g.*, a compound of the present invention together with a veterinary carrier.

[0089] Veterinary carriers are materials useful for the purpose of administering the composition and may be solid, liquid or gaseous materials which are otherwise inert or acceptable in the veterinary art and are compatible with the active ingredient. These veterinary compositions may be administered orally, parenterally or by any other desired route.

[0090] Compounds of the invention can also be formulated to provide controlled release of the active ingredient to allow less frequent dosing or to improve the pharmacokinetic or toxicity profile of the active ingredient. Accordingly, the

invention also provided compositions comprising one or more compounds of the invention formulated for sustained or controlled release.

[0091] The effective dose of an active ingredient depends at least on the nature of the condition being treated, toxicity, whether the compound is being used prophylactically (lower doses) or against an active disease or condition, the method of delivery, and the pharmaceutical formulation, and will be determined by the clinician using conventional dose escalation studies. The effective dose can be expected to be from about 0.0001 to about 100 mg/kg body weight per day. Typically, from about 0.01 to about 10 mg/kg body weight per day. More typically, from about 0.01 to about 5 mg/kg body weight per day. More typically, from about 0.05 to about 0.5 mg/kg body weight per day. For example, the daily candidate dose for an adult human of approximately 70 kg body weight will range from 1 mg to 1000 mg, or between 5 mg and 500 mg, and may take the form of single or multiple doses.

[0092] In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and a pharmaceutically acceptable carrier or excipient.

[0093] In yet another embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent, and a pharmaceutically acceptable carrier or excipient.

[0094] According to the present invention, the therapeutic agent used in combination with the compound of the present invention can be any agent having a therapeutic effect when used in combination with the compound of the present invention. For example, the therapeutic agent used in combination with the compound of the present invention can be any agent that is accessible to oxidative metabolism by cytochrome P450 enzymes, especially cytochrome P450 monooxygenase, *e.g.*, 1A2, 2B6, 2C8, 2C19, 2C9, 2D6, 2E1, 3A4,5,7, etc.

[0095] In another example, the therapeutic agent used in combination with the compound of the present invention can be any anti-viral agent, *e.g.*, anti-HIV, anti-HCV, etc., anti-bacterial agent, anti-fungal agent, immuno-modulator, *e.g.*, immunosuppressant, anti-neoplastic agent, chemotherapeutic agent, agents useful for treating cardiovascular conditions, neurological conditions, etc.

[0096] In yet another example, the therapeutic agent used in combination with the compound of the present invention can be any proton pump inhibitor, anti-epileptics, NSAID, oral hypoglycemic agent, angiotensin II, sulfonylureas, beta blocker, antidepressant, antipsychotics, or anesthetics, or a combination thereof.

[0097] In yet another example, the therapeutic agent used in combination with the compound of the present invention can be any 1) macrolide antibiotics, *e.g.*, clarithromycin, erythromycin, telithromycin, 2) anti-arrhythmics, *e.g.*, quinidine=>3-OH, 3) benzodiazepines, *e.g.*, alprazolam, diazepam=>30H, midazolam, triazolam, 4) immune modulators, *e.g.*, cyclosporine, tacrolimus (FK506), 5) HIV antivirals, *e.g.*, indinavir, nelfinavir, ritonavir, saquinavir, 6) prokinetic, *e.g.*, cisapride, 7) antihistamines, *e.g.*, astemizole, chlorpheniramine, terfenidine, 8) calcium channel blockers, *e.g.*, amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil, 9) HMG CoA reductase inhibitors, *e.g.*, atorvastatin, cerivastatin, lovastatin, simvastatin, or 10) steroid 6beta-OH, *e.g.*, estradiol, hydrocortisone, progesterone, testosterone.

[0098] In still yet another example, the therapeutic agent used in combination with the compound of the present invention can be any alfentanyl, aprepitant, aripiprazole, buspirone, cafergot, caffeine, TMU, cilostazol, cocaine, codeine-N-demethylation, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, LAAM, lidocaine, methadone, nateglinide, ondansetron, pimozide, propranolol, quetiapine, quinine, salmeterol, sildenafil, sirolimus, tamoxifen, taxol, terfenadine, trazodone, vincristine, zaleplon, or zolpidem or a combination thereof.

[0099] In one embodiment, the present application discloses pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, non-nucleoside inhibitors of HCV, CCR5 inhibitors, and combinations thereof, and a pharmaceutically acceptable carrier or excipient.

[0100] In another embodiment, the present application provides pharmaceutical compositions comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with at least one additional therapeutic agent selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, Racivir (±-FTC), D-d4FC, AVX754, tenofovir disoproxil fumarate, adefovir, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester,

tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, L-870810, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, aplaviroc, vicriviroc, and maraviroc, cyclosporine, FK-506, rapamycin, taxol, taxotere, clarithromycin, A-77003, A-80987, MK-639, saquinavir, VX-478, AG1343, DMP-323, XM-450, BILA 2011 BS, BILA 1096 BS, BILA 2185 BS, BMS 186,318, LB71262, SC-52151, SC-629 (N,N-dimethylglycyl-N-(2-hydroxy-3-(((4-methoxyphenyl)sulphonyl)(2-methylpropyl)amino)-1-(phenylmethyl)propyl)-3-methyl-L-valinamide), KNI-272, CGP 53437, CGP 57813 and U-103017 and a pharmaceutically acceptable carrier or excipient.

[0101] In yet another embodiment, the present application provides a combination pharmaceutical agent comprising:

a) a first pharmaceutical composition comprising a compound of the present invention, or a pharmaceutically acceptable salt, solvate, or ester thereof; and

b) a second pharmaceutical composition comprising at least one additional therapeutic agent selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, and other drugs for treating HCV, and combinations thereof.

Routes of Administration

[0102] One or more compounds of the invention (herein referred to as the active ingredients) are administered by any route appropriate to the condition to be treated. Suitable routes include oral, rectal, nasal, topical (including buccal and sublingual), vaginal and parenteral (including subcutaneous, intramuscular, intravenous, intradermal, intrathecal and epidural), and the like. It will be appreciated that the preferred route may vary with for example the condition of the recipient. An advantage of the compounds of this invention is that they are orally bioavailable and can be dosed orally.

Combination Therapy

[0103] In one embodiment, the compounds of the present invention can be used alone, e.g., for inhibiting cytochrome P450 monooxygenase. In another embodiment, the compounds of the present invention are used in combination with other active therapeutic ingredients or agents. Preferably, the other active therapeutic ingredients or agents are metabolized or accessible to the oxidative metabolism by cytochrome P450 enzymes, *e.g.*, monooxygenase enzymes such as 1A2, 2B6, 2C8, 2C19, 2C9, 2D6, 2E1, 3A4,5,7, etc.

[0104] Combinations of the compounds of the present invention are typically selected based on the condition to be treated, cross-reactivities of ingredients and pharmaco-properties of the combination. For example, when treating an infection (e.g., HIV or HCV), the compositions of the invention are combined with anti-infective agents (such as those described herein).

[0105] In one embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more anti-viral agents, *e.g.*, anti-HIV, anti-HCV, etc., anti-bacterial agents, anti-fungal agents, immuno-modulators, *e.g.*, immunosuppressant, anti-neoplastic agents, chemotherapeutic agents, agents useful for treating cardiovascular conditions, neurological conditions, etc.

[0106] In another embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more proton pump inhibitors, anti-epileptics, NSAIDs, oral hypoglycemic agents, angiotensin II, sulfonylureas, beta blockers, antidepressants, antipsychotics, or anesthetics, or a combination thereof.

[0107] In yet another embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more 1) macrolide antibiotics, *e.g.*, clarithromycin, erythromycin, telithromycin, 2) anti-arrhythmics, *e.g.*, quinidine=>3-OH, 3) benzodiazepines, *e.g.*, alprazolam, diazepam=>3OH, midazolam, triazolam, 4) immune modulators, *e.g.*, cyclosporine, tacrolimus (FK506), 5) HIV antivirals, *e.g.*, indinavir, nelfinavir, ritonavir, saquinavir, 6) prokinetic, *e.g.*, cisapride, 7) antihistamines, *e.g.*, astemizole, chlorpheniramine, terfenidine, 8) calcium channel blockers, *e.g.*, amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil, 9) HMG CoA reductase inhibitors, *e.g.*, atorvastatin, cerivastatin, lovastatin, simvastatin, or 10) steroid 6beta-OH, *e.g.*, estradiol, hydrocortisone, progesterone, testosterone.

[0108] In still yet another embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more compounds selected from the group consisting of alfentanyl, aprepitant, aripiprazole, buspirone, cafergot, caffeine=>TMU, cilostazol, cocaine, codeine- N-demethylation, dapsone, dextromethorphan, docetaxel, domperidone, eplerenone, fentanyl, finasteride, gleevec, haloperidol, irinotecan, LAAM,

lidocaine, methadone, nateglinide, odanestron, pimozide, propranolol, quetiapine, quinine, salmeterol, sildenafil, sirolimus, tamoxifen, taxol, terfenadine, trazodone, vincristine, zaleplon, and zolpidem or a combination thereof.

[0109] In still yet another embodiment, non-limiting examples of suitable combinations include combinations of one or more compounds of the present invention with one or more HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, and other drugs for treating HIV, interferons, ribavirin analogs, HCV NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, nucleoside or nucleotide inhibitors of HCV, non-nucleoside inhibitors of HCV, and other drugs for treating HCV.

[0110] More specifically, one or more compounds of the present invention may be combined with one or more compounds selected from the group consisting of 1) amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, GS-8374, PPL-100, DG35, and AG 1859, 2) a HIV non-nucleoside inhibitor of reverse transcriptase, *e.g.*, capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirene), efavirenz, BILR 355 BS, VRX 840773, UK-453061, and RDEA806, 3) a HIV nucleoside inhibitor of reverse transcriptase, *e.g.*, zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), GS-7340, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003), 4) a HIV nucleotide inhibitor of reverse transcriptase, *e.g.*, tenofovir and adefovir, 5) a HIV integrase inhibitor, *e.g.*, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), elvitegravir, L-870812, and L-870810, MK-0518 (raltegravir), BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011, 6) a gp41 inhibitor, *e.g.*, enfuvirtide, sifuvirtide, FB006M, and TRI-1144, 7) a CXCR4 inhibitor, *e.g.,* AMD-070, 8) an entry inhibitor, *e.g.,* SP01A, 9) a gp120 inhibitor, *e.g.,* BMS-488043 or BlockAide/ CR, 10) a G6PD and NADH-oxidase inhibitor, *e.g.,* immunitin, 11) a CCR5 inhibitor, *e.g.*, aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004, 12) other drugs for treating HIV, *e.g.,* BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040), 13) an interferon, *e.g.*, pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus IFN alpha (infergen), feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, locteron, Albuferon, Rebif, Oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and Pegylated IFN-beta, 14) a ribavirin analog, *e.g.*, rebetol, copegus, viramidine (taribavirin), 15) a NS5b polymerase inhibitor, *e.g.*, NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554, and GSK625433, 16) A NS3 protease inhibitor, *e.g.*, SCH-503034 (SCH-7), VX-950 (telaprevir), BILN-2065, BMS-605339, and ITMN-191, 17) an alpha-glucosidase 1 inhibitor, *e.g.*, MX-3253 (celgosivir), UT-231B, 18) hepatoprotectants, *e.g.,* IDN-6556, ME 3738, LB-84451, and MitoQ, 19) a non-nucleoside inhibitor of HCV, *e.g.*, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, A-831, GS-9190, and A-689; and 20) other drugs for treating HCV, *e.g.*, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497 (merimepodib).

[0111] It is also contemplated that the compounds of the present invention can be used with any other active therapeutic agent or ingredient which is appreciably metabolized by cytochrome P450 monooxygenase enzymes, e.g. cytochrome P450 monooxygenase 3A, thereby reducing the amount or rate at which the other active therapeutic agent or ingredient is metabolized, whereby the pharmacokinetics of the other active therapeutic agent or ingredient is improved. Such improvements can include elevating the blood plasma levels of the other therapeutic agent or ingredient or maintaining a more therapeutically effective blood plasma level of the other therapeutic active agent or ingredient -- compared to blood plasma levels of the other therapeutic agent or ingredient administered without the compound of the present invention.

[0112] It is also possible to combine any compound of the invention with one or more other active therapeutic agents in a unitary dosage form for simultaneous or sequential administration to a patient. The combination therapy may be administered as a simultaneous or sequential regimen. When administered sequentially, the combination may be administered in two or more administrations.

[0113] Co-administration of a compound of the invention with one or more other active therapeutic agents generally refers to simultaneous or sequential administration of a compound of the invention and one or more other active therapeutic agents, such that therapeutically effective amounts of the compound of the invention and one or more other active therapeutic agents are both present in the body of the patient.

[0114] Co-administration includes administration of unit dosages of the compounds of the invention before or after administration of unit dosages of one or more other active therapeutic agents, for example, administration of the compounds of the invention within seconds, minutes, or hours of the administration of one or more other active therapeutic agents. For example, a unit dose of a compound of the invention can be administered first, followed within seconds or minutes by administration of a unit dose of one or more other active therapeutic agents. Alternatively, a unit dose of one or more other therapeutic agents can be administered first, followed by administration of a unit dose of a compound of the invention within seconds or minutes. In some cases, it may be desirable to administer a unit dose of a compound of the invention first, followed, after a period of hours (e.g., 1-12 hours), by administration of a unit dose of one or more other active therapeutic agents. In other cases, it may be desirable to administer a unit dose of one or more other active therapeutic agents first, followed, after a period of hours(e.g., 1-12 hours), by administration of a unit dose of a compound of the invention.

[0115] The combination therapy may provide "synergy" and "synergistic effect", *i.e.* the effect achieved when the active ingredients used together is greater than the sum of the effects that results from using the compounds separately. A synergistic effect may be attained when the active ingredients are: (1) co-formulated and administered or delivered simultaneously in a combined formulation; (2) delivered by alternation or in parallel as separate formulations; or (3) by some other regimen. When delivered in alternation therapy, a synergistic effect may be attained when the compounds are administered or delivered sequentially, e.g., in separate tablets, pills or capsules, or by different injections in separate syringes. In general, during alternation therapy, an effective dosage of each active ingredient is administered sequentially, *i.e*. serially, whereas in combination therapy, effective dosages of two or more active ingredients are administered together.

[0116] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for improving the pharmacokinetics of a drug which is metabolized by cytochrome P450 monooxygenase, said method comprising administering to a patient treated with said drug, a therapeutically effective amount of the compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

[0117] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for improving the pharmacokinetics of a drug which is metabolized by cytochrome P450 monooxygenase.

[0118] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for improving the pharmacokinetics of a drug which is metabolized by cytochrome P450 monooxygenase 3A.

[0119] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for increasing blood plasma levels of a drug which is metabolized by cytochrome P450 monooxygenase.

[0120] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for increasing blood plasma levels of a drug which is metabolized by cytochrome P450 monooxygenase.

[0121] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for increasing blood plasma levels of a drug which is metabolized by cytochrome P450 monooxygenase 3A.

[0122] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for increasing blood plasma levels of a drug which is metabolized by cytochrome P450 monooxygenase, wherein the amount of the compound of the present invention administered is effective to inhibit cytochrome P450 monooxygenase.

[0123] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for inhibiting cytochrome P450 monooxygenase in a patient comprising administering to a patient in need thereof an amount of the compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450 monooxygenase.

[0124] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for inhibiting cytochrome P450 monooxygenase 3A in a patient comprising administering to a patient in need thereof an amount of the compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450 monooxygenase 3A.

[0125] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for inhibiting cytochrome P450 monooxygenase comprising contacting cytochrome P450 monooxygenase with an amount of the compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450

monooxygenase.

[0126] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for inhibiting cytochrome P450 monooxygenase 3A comprising contacting cytochrome P450 monooxygenase 3A with an amount of the compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, effective to inhibit cytochrome P450 monooxygenase 3A.

[0127] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for treating an HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of the compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, and CCR5 inhibitors.

[0128] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for treating an HIV infection comprising administering to a patient in need thereof a therapeutically effective amount of the compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, and GW640385X, DG17, PPL-100, DG35, AG 1859, capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, TMC-120, TMC-278 (rilpivirene), efavirenz, BILR 355 BS, VRX 840773,, UK-453061, RDEA806, zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, emtricitabine, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, fosalvudine tidoxil (formerly HDP 99.0003), tenofovir, adefovir, curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, L-870810, MK-0518 (raltegravir), BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011, enfuvirtide, sifuvirtide, FB006M, and TRI-1144, AMD-070, an entry inhibitor, SP01A, BMS-488043, BlockAide/ CR, a G6PD and NADH-oxidase inhibitor, immunitin, aplaviroc, vicriviroc, maraviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), CCR5mAb004, BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040).

[0129] In yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof for use in a method for treating an HCV infection comprising administering to the patient in need thereof a therapeutically effective amount of a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, in combination with a therapeutically effective amount of one or more additional therapeutic agents selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus IFN alpha (infergen), feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, locteron, albuferon, rebif, Oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and pegylated IFN-beta, rebetol, copegus, viramidine (taribavirin), NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554, GSK625433, SCH-503034 (SCH-7), VX-950 (telaprevir), BILN-2065, BMS-605339, ITMN-191, MX-3253 (celgosivir), UT-231B, IDN-6556, ME 3738, LB-84451, MitoQ, benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, A-831, A-689, zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497 (merimepodib).

[0130] In still yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in inhibiting cytochrome P450 monooxygenase in a patient.

[0131] In still yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in treating an HIV infection.

[0132] In still yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in increasing blood plasma levels of the drug which is metabolized by cytochrome P450 monooxygenase.

[0133] In still yet another embodiment, the present application provides a compound of the present invention, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, for use in improving the pharmacokinetics of a drug

which is metabolized by cytochrome P450 monooxygenase.

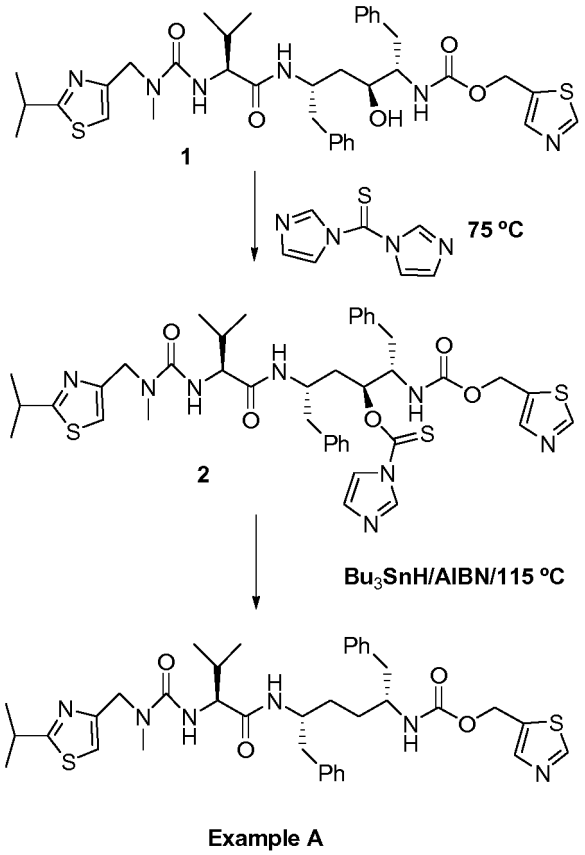
Examples

[0134] Examples provided below which do not relate to the appended claims are provided for reference only.

Preparation of Example A

[0135]

Scheme 1



Example A

Compound 2

[0136] To a solution of Compound 1 (ritonavir) (1.8 g, 2.5 mmol) in 1,2-dichloroethane (15 mL) was added 1,1'-thiocarbonyldiimidazole (890 mg, 5.0 mmol). The mixture was heated at 75 ºC for 6 hours and cooled to 25 ºC. Evaporation under reduced pressure gave a white solid. Purification by flash column chromatography (stationary phase: silica gel; eluent: EtOAc) gave Compound **2** (1.6 g). m/z: 831.1 $(M+H)^+$.

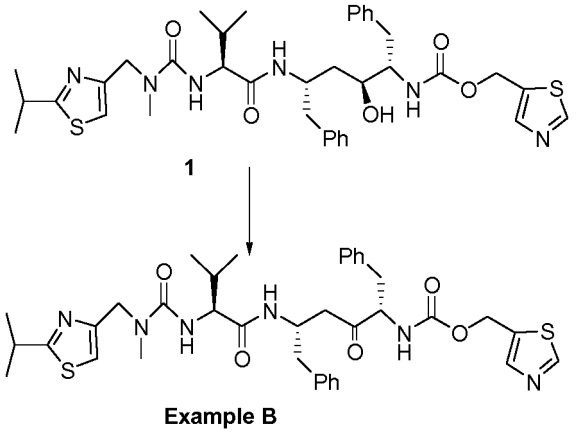
Example A

[0137] To the refluxing solution of tributyltin hydride (0.78 mL, 2.9 mmol) in toluene (130 mL) was added a solution of Compound **2** (1.6 g, 1.9 mmol) and 2,2'-azobisisobutyronitrile (31 mg, 0.19 mmol) in toluene (30 mL) over 30 minutes. The mixture was heated at 115 ºC for 6 hours and cooled to 25 ºC. Toluene was removed under reduced pressure. Purification by flash column chromatography (stationary phase: silica gel; eluent: hexane/EtOAc =1/10) gave Example **A** (560 mg). m/z: 705.2 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 8.79 (1 H, s), 7.82 (1 H, s), 7.26-7.05 (10 H, m), 6.98 (1 H, s), 6.28 (1 H, m), 6.03 (1 H, m), 5.27 (1 H, m), 5.23 (2 H, s), 4.45-4.22 (2 H, m), 4.17 (1 H, m), 3.98 (1 H, m), 3.75 (1 H, m), 3.25 (1 H, m), 2.91 (3 H, s), 2.67 (4 H, m), 2.36 (1 H, m), 1.6-1.2 (10 H, m), 0.85 (6 H, m).

Preparation of Example B

[0138]

Scheme 2



Example B

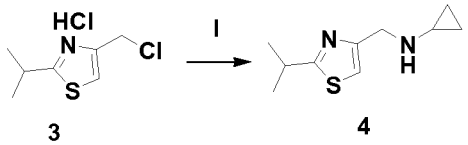
Example B

[0139] To a solution of Compound **1** (ritonavir) (98 mg, 0.136 mmol) in dichloromethane (4 mL) was added Dess-Martin periodinane (61 mg, 0.143 mmol). The mixture was stirred at room temperature for 6 hours. The mixture was then partitioned between dichloromethane and brine, the dichloromethane layer was separated, dried and evaporated to dryness. Purification with CombiFlash® (stationary phase: silica gel; eluent: 40-80% EtOAc/Hexane gradient) gave Example **B** as a white solid. Example **B** was further purified by trituration with MeOH/hexane to give 83 mg of a white solid. m/z: 719 $(M+H)^+$.

Preparation of Example C

[0140]

Scheme 3



I. cyclopropylamine, MeCN, rt

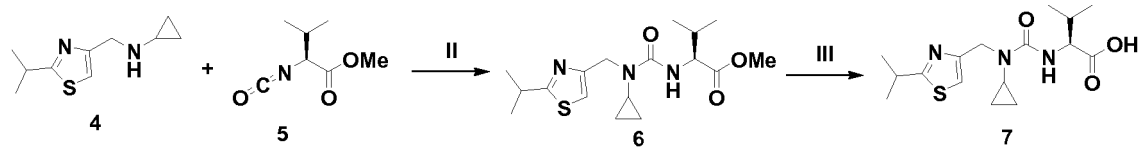
Compound 3

[0141] Compound **3** was prepared according to the procedures of J. Med. Chem. 1998, 41, 602, herein incorporated by reference in its entirety for all purposes.

Compound 4

[0142] A flask was charged with cyclopropylamine (8.2 mL, 117.8 mmol) at room temperature. A solution of Compound **3** (1 g, 4.71 mmol) in MeCN (8.5 mL) was added dropwise over 5 min. to produce a clear yellow solution that was allowed to stand at room temperature overnight. Volatiles were removed *in vacuo*, and the resulting residue was purified via silica gel chromatography (gradient elution, 0 to 50% EtOAc/hexane) to afford 0.65 g (70%) of **4** as a yellow liquid (LC/MS *m/z* 197 $(M+H)^+$; 218 $(M+Na)^+$).

Scheme 4



II. rt, DCM; III. 1M LiOH, THF/H_2O

Compound 5

[0143] Compound **5** was purchased from Aldrich or alternatively prepared according to the procedures of J. Org. Chem. 1994, 59, 1937, herein incorporated by reference in its entirety for all purposes.

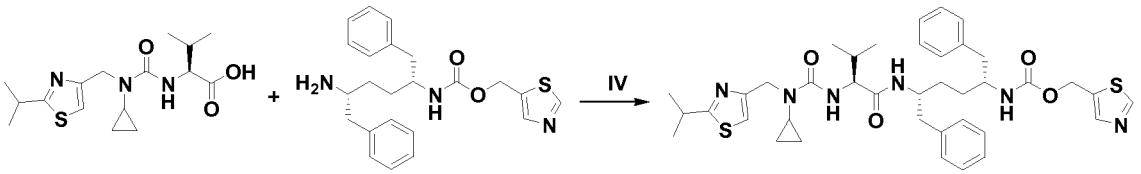
Compound 6

[0144] To a solution of Compound **4** in DCM (3 mL) at room temperature was added 5 (0.1 mL, 0.695 mmol). The resulting clear solution was allowed to stand at room temperature for 2 h. The solvent was removed *in vacuo*, and the residue was chromatographed directly using silica gel chromatography (gradient elution, 0 to 50% EtOAc/hexane) to produce 0.218 g (89%) of **6** (LC/MS *m/z* 354 $(M+H)^+$; 729 $(2M + Na)^+$) as a colorless glass.

Compound 7

[0145] Compound **6** was taken up in THF (5 mL) at room temperature, and LiOH (1 M in H_2O) was added. The resulting reaction mixture was then stirred vigorously for 1.5 h. The reaction mixture was acidified with 1 M HCl to a pH of 3 (monitored using pH test strips). The acidified reaction mixture was then extracted several times with EtOAc. The combined organic phases were washed with brine, dried over anhydrous Na_2SO_4, and concentrated *in vacuo* to produce 0.20 g (quantitative yield) of **7** (LC/MS *m/z* 340 $(M+H)^+$) as a colorless film. This material was used without further purification.

Scheme 5



IV. EDC, HOBt, DIPEA, THF

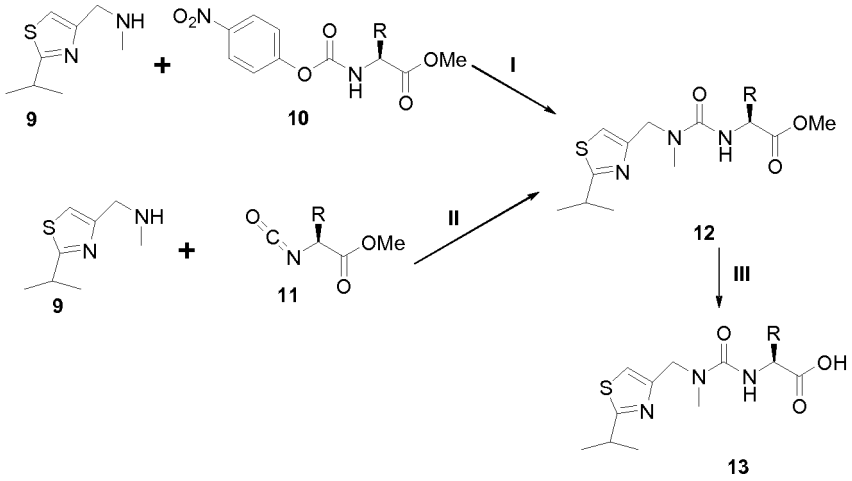
Example C

[0146] Compounds **7** (0.034 g, 0.100 mmol) and 8, (0.034 g, 0.083 mmol) were diluted in THF (2 mL) at room temperature. To the resulting solution were added *N,N*-diisopropylethylamine (0.022 mL, 0.125 mmol), EDC (0.018 mL, 0.099 mmol) and HOBt (0.013 g, 0.099 mmol). The solution was then allowed to stand overnight at room temperature. The solvent was removed *in vacuo* and the residue was taken up in MeCN (0.5 mL) and passed through an Acrodisc LC13 PVDF filter (0.45 μM) prior to purification by preparatory HPLC to afford 0.043 g (71%) of Example **C** as a fluffy white solid. (^{1}H-NMR (300 MHz, $CDCl_3$) δ 8.79 (s, 1H); 7.82 (s, 1H); 7.27-7.02 (m, 10 H); 6.81 (s, 1H); 5.97 (br d, *J* = 8.7 Hz, 1H); 5.76 (br d, *J* = 7.2 Hz, 1H); 5.21 (dt, *J* = 7.5, 12.6 Hz, 2H); 5.02, br d, *J* = 8.4 Hz, 1H); 4.58 (s, 2H); 4.16 (m, 1H); 3.99 (br t, *J* = 6.6 Hz, 1H); 3.79 (m, 1H); 3.27 (pent, *J* = 6.6 Hz, 1H); 2.85-2.50 (m, 3H); 2.23 (m, 1H); 1.82 (br s, 2H); 1.60-1.22 (m, 4H); 1.36 (d, *J* = 6.6 Hz, 6H); 0.91 (d, *J* = 6.6 Hz, 3H); 0.90-0.7 (m, 4H); 0.80 (d, *J* = 6.6 Hz, 3H); LC/MS *m/z* 731 (M^+)).

Preparation of Examples D-I

[0147]

Scheme 6



I. Et_3N/DMAP/THF/65 °C; II. CH_2Cl_2/25 °C; III. a. NaOH/dioxane/H_2O; b. HCl

a: R = H
b: R = CH_3
c: R= CH_2CH_3
d: R = CH_2OBn
e: R = CH(O-t-Bu)CH_3
f: R = CH(OH)CH_3

Compound 9

[0148] Compound **9** was prepared according to the procedures of J. Med. Chem. 1998, 41, 602.

Compund 10

[0149] The structures of Compound **10** were prepared according to the procedures of J. Med. Chem. 1998, 41, 602.

Compund 11

[0150] The structures of Compound **11** were purchased from Aldrich or prepared according to the procedures of J. Org. Chem. 1994, 59, 1937.

Compound 12

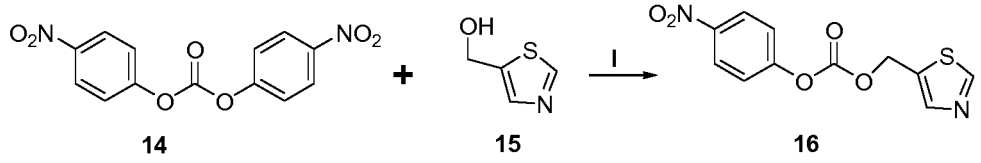
[0151] Method 1: To a solution of Compound **9** (0.8 mmol) in THF (2 mL) was added a carbamate of Compound **10** (0.6 mmol), followed by DMAP (16 mg) and triethylamine (0.25 mL). The resulting mixture was heated at 70 oC for two hours and diluted with EtOAc. The organic phase was separated, and washed sequentially with saturated aqueous Na_2CO_3, water, and brine, then concentrated under reduced pressure. Purification of the residue by flash column chromatography (silica gel, 1/1 - 1/3 hexanes/EtOAc gradient) gave compounds of Structure **12**.

[0152] Method 2: To a solution of Compound **9** (2.4 mmol) in CH_2Cl_2 (2 mL) was added an isocyanate of Compound **11** (2 mmol). The resulting mixture was stirred for 4 hours and concentrated. Purification of the residue by flash column chromatography (silica gel, hexane/EtOAc 1/1 - 1/3) gave structures of Compound **12**.

Compound 13

[0153] To a solution of structures of Compound **12** (1.8 mmol) in dioxane (8 mL) and water (8 mL) was added sodium hydroxide (3.6 mmol). The resulting reaction mixture was stirred for 1 hour and acidified with HCl in dioxane (3.6 mmol). The reaction mixture was extracted with EtOAc and the organic phase was dried with anhydrous $MgSO_4$. Concentration of the dried organic phase gave structures of Compound **13**.

Scheme 7



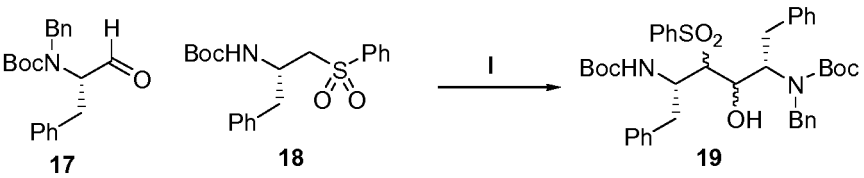
14 15 16

I. Et_3N/DCM

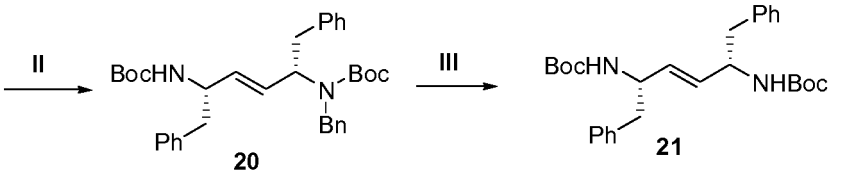
Compound 16

[0154] To a solution of Compound **15** (obtained commercially from Molekula) (17 mmol) in DCM (40 mL) was added Compound **14** (19 mmol), followed by triethylamine (26 mmol). The resulting reaction mixture was stirred for 12 hour and concentrated under reduced pressure. The reaction mixture was diluted with EtOAc and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The solvent was removed under reduced pressure. Purification of the residue by flash column chromatography (silica gel, eluent: hexanes/EtOAc = 1/1) gave Compound **16** (4.7 g).

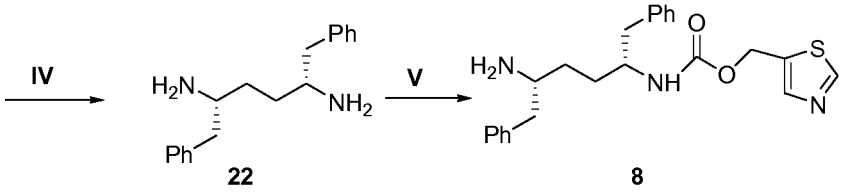
Scheme 8



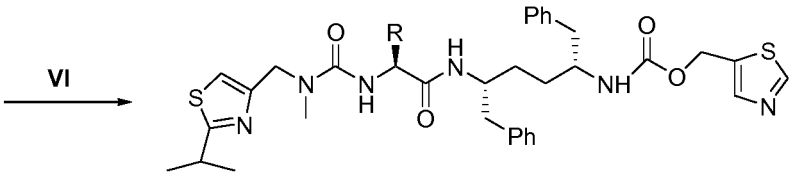
17 18 19



20 21



22 8



Examples:
D: R = H
E: R = CH_3
F: R = CH_2CH_3
G: R = CH_2OBn
H: R = $CH(O\text{-}t\text{-}Bu)CH_3$
I: R = $CH(OH)CH_3$

I. a. n-BuLI/-78 C; b.i-$Bu_2Al(OMe)$; II. a. Ac_2O/pyridine; b. Na-Hg/MeOH/THF; III. Na/NH_3/-33 C; IV. a. H_2/10%Pd/C; b. TFA/DCM; V. 16/Et_3N; VI. acid of structure 13/EDC/HOBt

Compound 17

[0155] Compound **17** was prepared according to the procedures of Tetrahedron 1997, 53, 4769, herein incorporated by reference in its entirety for all purposes.

Compound 18

[0156] Compound **18** was prepared according to the procedures of J. Org. Chem. 1987, 52, 3759, herein incorporated by reference in its entirety for all purposes.

Compound 19

[0157] A suspension of Compound **18** (7.4 mmol) in THF (200 mL) was heated under reflux until a clear solution was obtained. The solution was cooled to -78 ºC and n-butyllithium (14.8 mmol) was added dropwise to provide a solution of the dianion of sulfone **18**.

[0158] To a DIBAL-H solution (7.8 mmol) at 0 ºC was added a solution of MeOH (7.8 mmol) in THF (5 mL). The mixture was stirred for 5 minutes and cooled to78 ºC. A solution of Compound **17** (6.6 mmol) in THF (5 mL) was added to the above DIBAL-H/MeOH solution, and the resulting reaction mixture was stirred for another 5 minutes. The resulting solution of aldehyde complexes was transferred to solution of the dianion of sulfone **18**. The resulting mixture was stirred at -78 ºC for 30 minutes, quenched with an aqueous solution of NH_4Cl, and warmed to 25 ºC. The mixture was then extracted with EtOAc, and concentrated to give Compound **19** as a mixture of diastereomers. (m/z 737.3 $(M+Na)^+$.

Example 20

[0159] To a solution of Compound **19** in DCM (20 mL) was added Ac_2O (1.5 mL), followed by pyridine (3 mL). The resulting mixture was stirred for 12 hours and concentrated. The concentrate was dissolved in MeOH (30 mL) and cooled to 0 ºC. NaH_2PO_4 (4.9 g) was added to the solution, followed by freshly prepared Na-Hg (6%, 6 g). The resulting mixture was warmed to 25 ºC and stirred for 12 hours. Water (50 mL) was then added, and the mixture was filtered and concentrated. The concentrate was diluted with EtOAc and washed with brine. The organic phase was concentrated. Purification by flash column chromatography (silica gel, eluent: hexanes/EtOAc = 10/1) gave Compound **20** (1.4 g).

Compound 21

[0160] To liquid ammonia (25 mL) at -33 ºC was added a solution of Compound **20** (1.4 g) in THF (2.5 mL). Sodium was slowly added until the blue color of the solution persisted. The resulting mixture was stirred for 1 hour. Solid NH_4Cl (6 g) was then added slowly, the mixture was warmed to 25 ºC, and the ammonia was evaporated. The mixture was diluted with EtOAc, and washed sequentially with water and brine. The solvent was removed under reduced pressure. Purification of the resulting residue by flash column chromatography (silica gel, eluent: hexanes/EtOAc = 5/1) gave Compound **21** (1.15 g).

Compound 22

[0161] A mixture of Compound **21** (1.15 g) and 10%Pd/C (160 mg) in MeOH (20 mL) was hydrogenated for 12 hours. CELITE was added and the resulting mixture was stirred for 5 minutes. The mixture was then filtered and concentrated to give an intermediate (1 g). The intermediate (700 mg) was dissolved in DCM (20 mL) and TFA (4 mL), and the resulting mixture was stirred for 4 hours, then concentrated under reduced pressure. The concentrated mixture was diluted with EtOAc, and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. Concentration of the washed EtOAc mixture gave Compound **22** (420 mg).

Compound 8

[0162] To a solution of Compound **22** (1.57 mmol) in CH_3CN (16 mL) was added Compound **16** (1.57 mmol), followed by diisopropylethylamine (3.14 mmol). The resulting mixture was stirred for 12 hours. The mixture was then diluted with EtOAc, and washed sequentially with saturated aqueous Na_2CO_3, water and brine. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 25% - 100% CH_3CN in water) gave Compound **8** (460 mg).

Example D

[0163] To the solution of Compound **13a** (R= H; 0.08 mmol) and Compound **8** (0.06 mmol) in THF (1 mL) were added HOBt (15 mg), EDC (26 mg), and disopropylethylamine (0.25 mL). The mixture was stirred for 12 hours and concentrated. Purification by reverse phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 25% - 100% CH_3CN in water) gave Example **D** (27 mg). m/z 663.1 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 8.79 (1 H, s), 7.83 (1 H, s), 7.25-7.04 (10 H, m), 6.98 (1 H, s), 6.25 (1 H, m), 5.25 (3 H, m), 4.40 (2 H, s), 4.12 (1 H, m), 3.8 (3 H, m), 3.22 (1 H, m), 2.95 (3 H, s), 2.70 (4 H, m), 1.60 (4 H, m), 1.26 (6 H, d, J = 7 Hz).

Example E

[0164] Example **E** was prepared following the procedure for Example **D** (30 mg), except that Compound **13b** was used instead of Compound **13a**. m/z 677.1
$(M+H)^+$.

Example F

[0165] Compound **F** was prepared following the procedure for Example D (40 mg), except that Compound **13c** was used instead of Compound **13a**. m/z 691.2 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) b 8.80 (1 H, s), 7.83 (1 H, s), 7.25-7.06 (10 H, m), 6.98 (1 H, s), 6.35 (1 H, m), 6.23 (1 H, m), 5.24 (2 H, s), 5.12 (1 H, m), 4.34 (2 H, s), 4.10 (2 H, m), 3.78 (1 H, m), 3.23 (1 H, m), 2.90 (3 H, s), 2.68 (4 H, m), 1.90 (2 H, m), 1.7-1.4 (4 H, m), 1.36 (6 H, d, J = 7.0 Hz), 0.90 (3 H, t, J = 7.3 Hz)

Example G

[0166] Example G was prepared following the procedure for Example **D** (84 mg), except that Compound **13d** was used instead of Compound **13a**. m/z 783.2
$(M+H)^+$.

Example H

[0167] Example **H** was prepared following the procedure for Example **D** (90 mg), except that Compound **13e** was used instead of Compound **13a**. m/z 763.2
$(M+H)^+$.

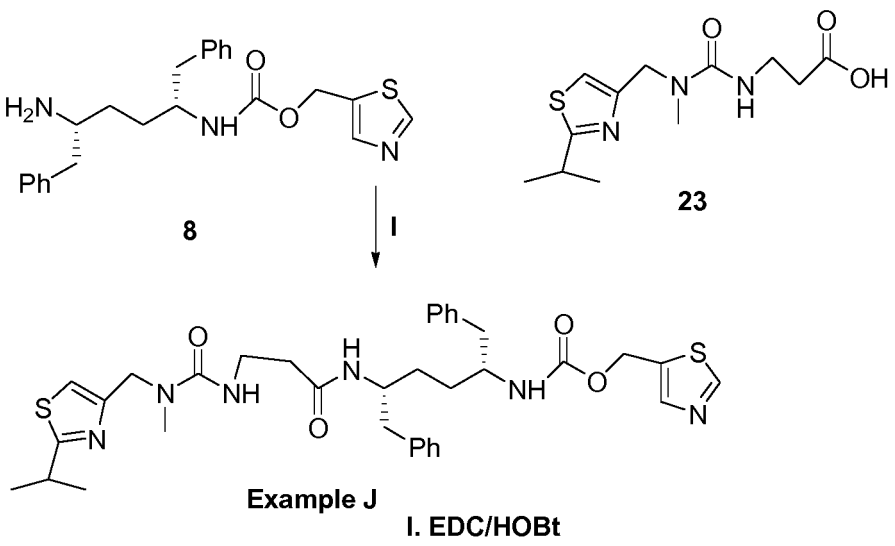
Example I

[0168] Example **H** (24 mg) was dissolved in TFA (2 mL) and the mixture was stirred for 12 hours, then concentrated, Purification by reverse phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 25% - 100% CH_3CN in water) gave Example I (14 mg). m/z 707.2 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) b 8.82 (1 H, s), 7.85 (1 H, s), 7.26-7.04 (10 H, m), 7.0 (1 H, s), 5.25 (2 H, s), 4.86 (1 H, m), 4.56 (1 H, m), 4.37 (2 H, m), 4.13 (1 H, m), 4.06 (1 H, m), 3.86 (1 H, m), 3.32 (1 H, m), 2.99 (3 H, s), 2.8-2.6 (4 H, m), 1.6-1.4 (4 H, m), 1.37 (6 H, m), 1.15 (3 H, m).

Preparation of Example J

[0169]

Scheme 9



Example J

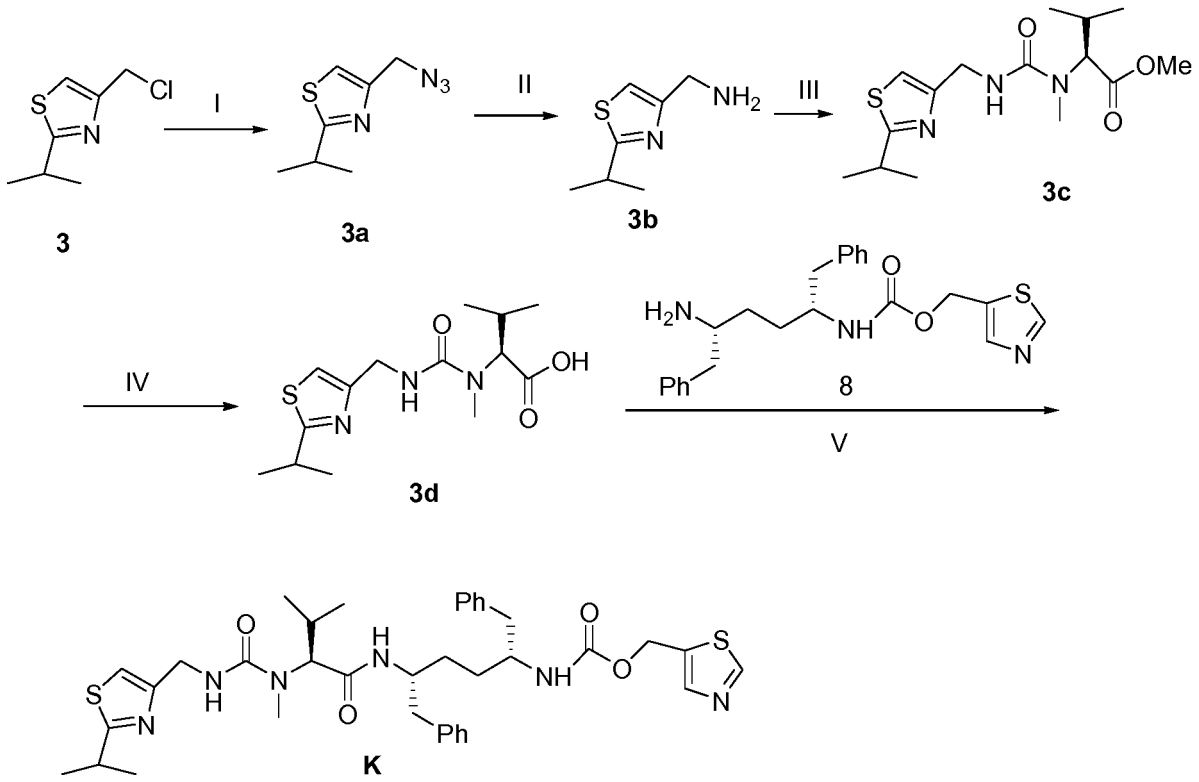
[0170] Compound **23** was prepared following the procedure for Compound **13**, with the exception that methyl 3-isocyanatopropionate was used instead of Compound **11**.

[0171] Example **J** was prepared following the procedure for Example **D** (37 mg), except that Compound **23** was used instead of Compound **13a**. m/z 677.2 $(M+H)^+$.

Preparation of Example K

[0172]

Scheme 10



1. NaN_3/DMF; II. PPh_3/H_2O; III. a. $Cl_3COCOOCCl_3$; b. HCl-$NH_2CHiPrCO_2Et$; IV. a. NaOH; b. HCl; V. EDC/HOBt/compound 8

Example K

Compound 5a

[0173] Compound 5a was prepared following the literature procedure of Synthesis 823, 1976, herein incorporated by reference in its entirety for all purposes.

Compound 5b

[0174] To the solution of Compound **5a** (700 mg, 3.9 mmol) in THF (10 mL) was added water (69 μL, 3.9 mmol), followed by triphenylphosphine (1.06 g, 4.0 mmol). The mixture was stirred for 12 hours. Solvents were removed and the mixture was dried to give Compound **5b,** which was used for next step without further purification.

Compound **5c**

[0175] To a solution of triphosgene (110 mg, 0.37 mmol) in CH_2Cl_2 (2 mL) at 0 C was added a solution of Compound **5b** (1 mmol) and $iPrNEt_2$ (0.38 mL, 2.2 mmol) in CH_2Cl_2 (3.5 mL) over 30 minutes period. The mixture was stirred for 30 minutes, and a solution of amino N-methyl leucine methyl ester HCl salt (182 mg, 1 mmol) and $iPrNEt_2$ (0.34 mL, 2.2 mmol) in CH_2Cl_2 (2 mL) was added. The mixture was stirred for 12 hours, and diluted with EtOAc. The solution was washed with sat. Na_2CO_3 (2x), water (2x), and brine, and dried over Na_2SO_4. Concentration and purification with silica gel flash column gave Compound **5c** (300 mg).

Compound 5d

[0176] Compound **5d** was prepared following the procedure for Compound **13,** with the exception that Compound **5c** was used instead of Compound **12.**

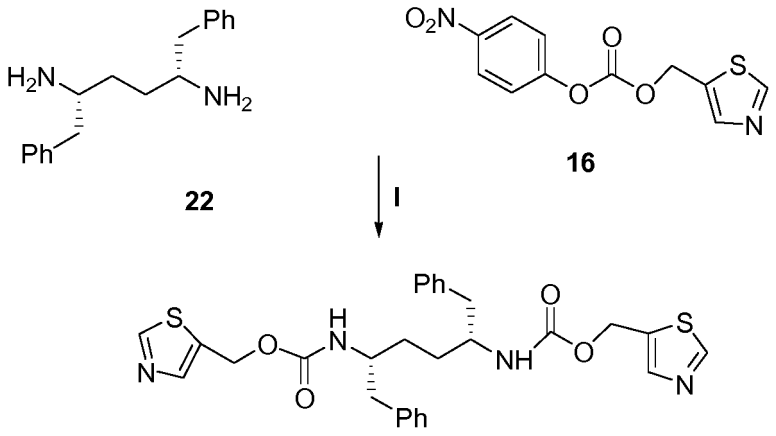
Example K

[0177] Example **K** was prepared following the procedure for Example **D** (7 mg), except that Compound **5d** was used instead of Compound **13a.** m/z 705.2 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ 8.8 (1H, m), 7.86 (1 H, s), 7.26-6.8 (11 H, m), 6.10 (1 H, m), 5.5-5.10 (4 H, m), 4.46 (2 H, m), 4.2-3.75 (3 H, m), 3.25 (1 H, m), 2.82/2.4 (3 H), 2.8-2.5 (4 H, m), 2.17 (1 H, m), 1.7-1.2 (10 H, m), 0.8 (6 H, m).

Preparation of Example L

[0178]

Scheme 11



Example L

I. Et_3N

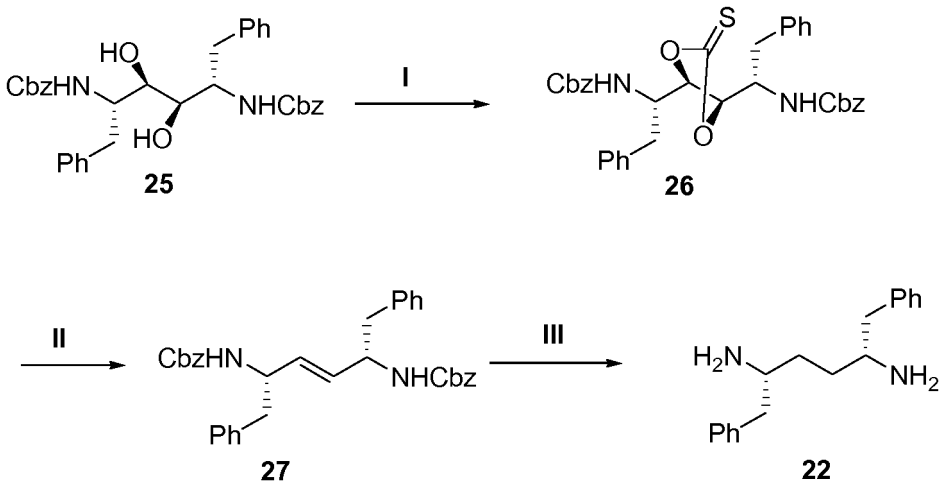
Example L

[0179] To a solution of Compound **22** (1.57 mmol) in CH_3CN (16 mL) was added Compound **16** (3.14 mmol), followed by triethylamine (4.71 mmol). The resulting mixture was stirred for 12 hours. The reaction mixture was diluted with EtOAc and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The solvent was removed under reduced pressure. Purification of the residue by flash column chromatography (silica gel, eluent: hexanes/EtOAc = 1/1) gave Example **L** (460 mg). m/z 551.2 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) b 8.81 (2 H, s), 7.85 (2 H, s), 7.26-7.0 (10 H, m), 5.24 (4 H, s), 4.50 (2 H, m), 3.87 (2 H, m), 2.73 (4 H, m), 1.4-1.2 (4 H, m).

Alternate Preparation of Compound 22

[0180]

Scheme 12



I. TCDI/THF/65 °C; II. $P(OEt)_3$/160 °C; III. 10%Pd/C/i-PrOH/EtOAc

Compound 25

[0181] Compound **25** was prepared following the literature procedure described in J. Org. Chem. 1996, 61, 444 (herein incorporated by reference in its entirety), except that the L-isomer was prepared instead of the D-isomer.

Compound 26

[0182] A mixture of Compound **25** (7.4 g) and 1,1'-thiocarbonyldiimidaxole (4.5 g) in THF (260 mL) was heated at 65ºC for 54 hours. Solvent was removed from the mixture under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc = 1/1) gave Compound **26** (7.33 g).

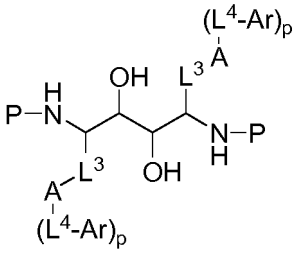
Compound 27

[0183] The mixture of Compound **26** (7.3 g) and triethylphosphite (100 mL) was heated at 160ºC for 4 hours. Excess reagents were removed under reduced pressure. Purification by flash column chromatography (silica gel, hexanes/EtOAc = 3/1) gave Compound **27** (5 g).

Compound 22

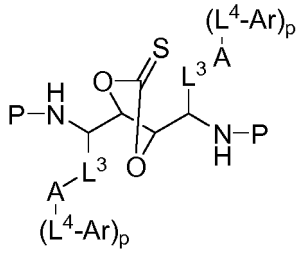
[0184] A mixture of Compound **27** (250 mg) in i-PrOH/EtOAc (5mL/5mL) was hydrogenated for 14 hours in the presence of 10%Pd/C (75 mg). CELITE was added to the mixture, and the mixture was stirred for 5 minutes. Filtration and evaporation of solvents gave Compound **22** (116 mg).

[0185] The skilled practitioner will recognize that the procedure outlined in Scheme 12 can be used to prepare a variety of 1,4-substituted 1,4-diamines analogous to Compound **22.** For example, an amine-protected 2,3-dihydroxy-1,4-diamine analogous to Compound **25** can be prepared:



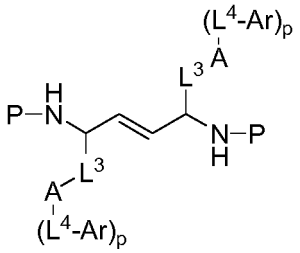
Analogs of Compound 25

wherein L^3, A, Ar, and P are as defined herein, and protecting group "P" is any amine protecting group described in described in Protective Groups in Organic Synthesis, Theodora W. Greene and Peter G. M. Wuts (John Wiley & Sons, Inc., New York, 1999, ISBN 0-471-16019-9), which is herein incorporated by reference in its entirety for all purposes. The analogs of Compound **25** can then be transformed, according to the methods outlined in Scheme **12,** to form analogs of Compound **26:**



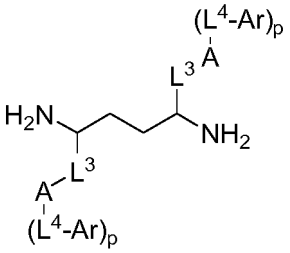
Analogs of Compound **26;**

analogs of Compound 27:



Analogs of Compound **27;**

and analogs of Compound 22:

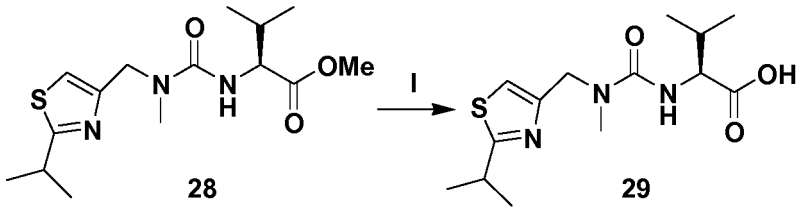


Analogs of Compound **22.**

Preparation of Examples M and N

[0186]

Scheme 13



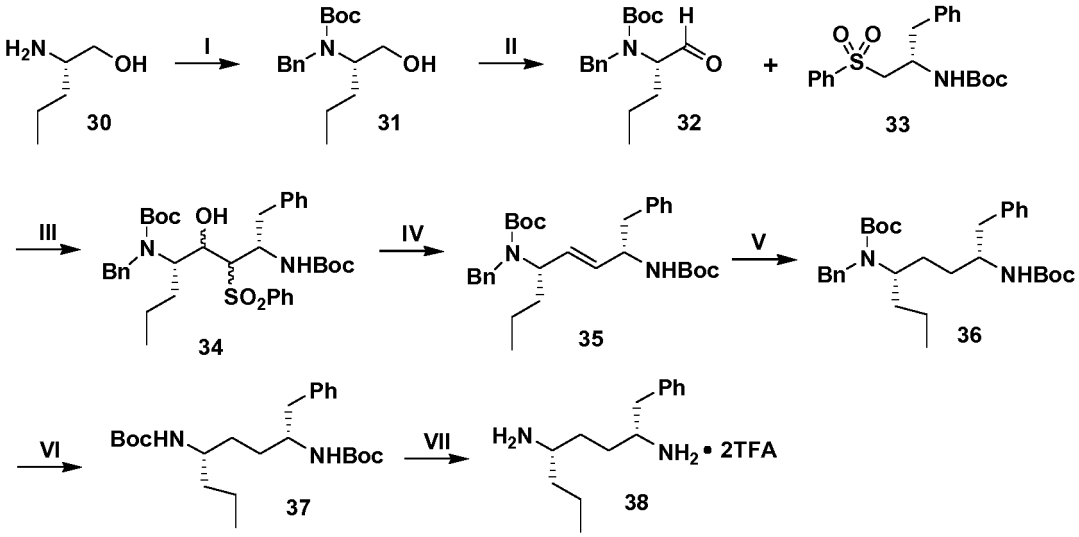
I. a. LiOH, THF/H_2O, 25 °C; b. HCl

Compound 29

[0187] Compound **28** was prepared using a procedure similar to that used to prepare Compound **6** (described in Scheme 4) except that Compound **9** was used instead of Compound **4.**

[0188] To a solution of Compound **28** (0.757 g, 2.31 mmol) in THF (9 mL) at room temperature was added freshly prepared 1M LiOH (4.6 mL, 4.6 mmol). After 1.5 h, 1 M HCl (7 mL, 7 mmol) was added and the reaction mixture extracted thoroughly with EtOAc (5 X 15mL). The combined organic layers were dried over anhydrous Na_2SO_4 and the volatiles removed *in vacuo* to afford 0.677 g (93%) of Compound **29** as a colorless glassy solid (LC/MS *m/z* 314.0 $(M+H)^+$) that was used in the following procedures without further purification.

Scheme 14



I. a. PhCHO, MeOH; b. $NaBH_4$; c. Boc_2O, THF/H_2O. II. Pyr•SO_3, Et_3N, DMSO 0 °C. III. *n*-BuLi, MeOAl(*i*-Bu)$_2$, THF, -78 °C. IV. a. Ac_2O, pyr, CH_2Cl_2, b. 6% Na/Hg, Na_2HPO_4, MeOH. V. H_2, 10% Pd/C, MeOH. VI. Na/NH_3, THF, -35 °C. VII. 20% TFA/DCM.

Compound 30

[0189] Compound **30** was purchased from Aldrich Chemical Co., and used without further purification.

Compound 31

[0190] To a solution of Compound **30** (8.25 g, 80 mmol) in MeOH (50 mL), was added benzaldehyde (8.1 mL, 80 mmol) and the resulting solution was allowed to stir at room temperature. After 2 h, the reaction mixture was cooled to 0 °C and $NaBH_4$ (3.33 g, 88 mmol) was added in portions. After allowing the reaction mixture to warm to room temperature over 2 h, glacial acetic acid (2 mL) was added. The resulting viscous solution was concentrated *in vacuo*. EtOAc and H_2O (50 mL each) were added and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with saturated $NaHCO_3$, brine, and concentrated *in vacuo*. The resulting material was taken up in THF (25 mL)

and H_2O (25 mL) at room temperature and Boc_2O (15.1 g, 69.2 mmol) was added to produce an opaque suspension that was stirred vigorously for 2 h at room temperature. THF was removed *in vacuo*, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine and dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. Chromatography on SiO_2 (3/1 Hex/EtOAC) afforded 18.5 g (79%) of Compound **31** as a colorless oil (LC/MS *m*/*z* 293.9 $(M+H)^+$.

Compound 32

[0191] Compound **31** (5.95 g, 20.3 mmol) and Et_3N (9.9 mL, 71 mmol) were diluted in DMSO (65 mL) and allowed to age at room temperature for 30 min before cooling to 0 °C. Pyridine•SO_3 was added in one portion and the reaction mixture was maintained at 5 °C to prevent freezing. After 45 min, the reaction mixture was poured into icewater and extracted with EtOAc. The combined organic layers were washed with saturated $NaHCO_3$, H_2O, and dried over anhydrous $MgSO_4$ prior to concentration *in vacuo* (bath temperature 25 °C) to produce 4.39 g (74%) of Compound **32** as a clear, yellow colored oil that was used without further purification. ^{1}H-NMR ($CDCl_3$, 300 MHz) δ (major rotamer) 9.36 (br s, 1H); 5.01 (d, *J* = 15 Hz, 1H); 4.12 (d, *J* = 15 Hz, 1H); 3.45 (m, 1H); 2.04-1.88 (m, 1H); 1.80-1.58 (m, 1H); 1.54-1.20 (m, 2H); 1.47 (s, 9H); 0.91 (t, *J* = 7.2 Hz, 3H). (minor rotamer) 9.46 (br s, 1H); 4.71 (d, *J* = 15 Hz, 1H); 4.20 (d, *J* = 15 Hz, 1H); 3.78 (m, 1H); 2.04-1.88 (m, 1H); 1.80-1.58 (m, 1H); 1.54-1.20 (m, 2H); 1.47 (s, 9H); 0.91 (t, *J* = 7.2 Hz, 3H)

Compound 34

[0192] A suspension of Compound **33** (6.23 g, 16.6 mmol) in THF (500 mL) was heated under reflux until a homogeneous solution was obtained. The solution was cooled to -78 °C and 1.6M *n*-BuLi (19.7 mL, 31.5 mmol) was introduced to produce a clear yellow solution. Meanwhile, DIBAL-OMe was prepared by dilution of DIBAL-H (1M in hexanes, 18.1 mL, 18.1 mmol) in THF (8 mL) and cooling to 0 °C prior to addition of MeOH (0.73 mL, 18.1 mmol). This solution was allowed to age while Compound **32** (4.39 g, 15.1 mmol) was diluted in THF (15 mL) and cooled to -78 °C. The DIBAL-OMe solution was cannulated to the solution of Compound **32** and allowed to age for 5 min prior to cannulation to the sulfur dianion solution. The resulting clear yellow solution was allowed to age at -78 °C for 1h. The reaction was quenched by addition of saturated NH_4Cl (100 mL) at -78 °C and allowed to warm to room temperature. Water was added until all precipitated solids were dissolved and the layers separated. The THF layer was concentrated *in vacuo* while the aqueous layer was extracted with EtOAc. The recombined organic layers were washed with brine, and the resulting emulsion was treated with solid NaOH until homogeneous bilayers resulted. The aqueous layer was extracted with EtOAc and the combined organics dried over anhydrous Na_2SO_4. Concentration *in vacuo* produced 9.57 g (95%) of Compound **34** as an amorphous white solid (LC/MS *m*/*z*: 689.3 $(M+Na)^+$) that was used in the following procedures without further purification.

Compound 35

[0193] Crude Compound **34** was suspended in CH_2Cl_2 (65 mL) followed by addition of pyridine (6.7 mL, 83 mmol) and acetic anhydride (3.5 mL, 36.5 mmol). The resulting solution was allowed to age at room temperature overnight. MeOH (6 mL) was added and after 10 min, the reaction was poured into brine. Addition of water produced a bilayer that was separated and the aqueous phase was repeatedly extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to produce 8.95 g (88%) of a white solid that was immediately taken up in MeOH (100 mL). Na_2HPO_4 (11.4 g, 80.3 mmol) was added and the resulting slurry was cooled to 0 °C prior to addition of Na-Hg (6%, 14.5 g, 37.8 mmol) in portions. After aging at room temperature overnight, H_2O (30 mL) was added and the reaction was filtered through a celite pad. MeOH was removed *in vacuo* and the aqueous residue was extracted with EtOAc. The combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo* to a yellow oil that was purified by chromatography on SiO_2 (0-15% EtOAc/hexanes) to afford 2.14 g (34%) of Compound **35** as a colorless oil (LC/MS *m*/*z*: 531.2 $(M+Na)^+$).

Compound 36

[0194] Compound **35** (1.73 g, 3.4 mmol) was diluted in MeOH (7.5 mL) and 10% Pd/C (0.36 g, 0.34 mmol) was added. The atmosphere was replaced with a H_2 balloon and the reaction mixture allowed to age at room temperature. After 2 h, the reaction mixture was filtered through a pad of celite, the filtrate was washed several times with MeOH, and the combined organic layers were concentrated *in vacuo* to afford 1.45 g (83%) of Compound **36** as a colorless oil (LC/MS *m*/*z*: 533.2 $(M+Na)^+$) that was used in the following procedures without further purification.

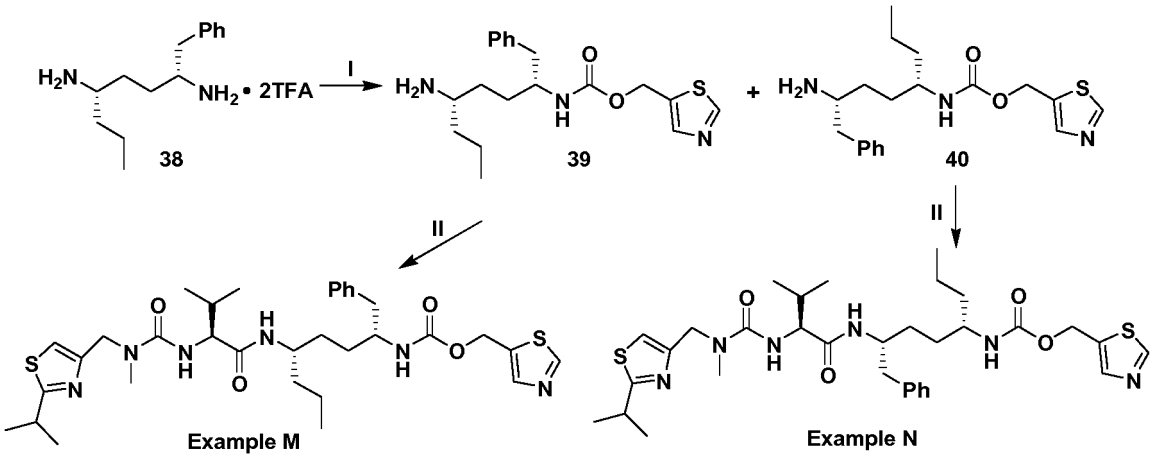
Compound 37

[0195] Compound **36** (0.528 g, 1.03 mmol) was diluted in THF (3 mL) and added to liquefied ammonia (approx. 20 mL) at -35 °C. Small pieces of Na were added until a blue color persisted. After 1.5 h, solid NH_4Cl was added in portions until the remaining Na was destroyed and the ammonia was allowed to escape at ambient temperature. Water and EtOAc (20 mL each) were added, and the aqueous layer was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to afford 0.395 g (91%) of Compound **37** as an amorphous white solid that was used without further purification in the following procedures (LC/MS *m/z*: 421.1 $(M+H)^+$; 443.2 $(M+Na)^+$).

Compound 38

[0196] Compound **37** (0.362 g, 0.861 mmol) was diluted in CH_2Cl_2 (3.2 mL). Trifluoroacetic acid (0.8 mL) was added and the clear solution was allowed to age overnight. Following concentration *in vacuo*, the residue was azeotroped with toluene several times to remove residual TFA. 0.382 g (99%) of the bis-trifluoroacetate salt of Compound **38** was collected as a colorless oil that was used without further purification (LC/MS *m/z*: 221.1$(M+H)^+$).

Scheme 15



I. carbonate 16, DIPEA, MeCN; II. acid 29, EDC, HOBt, DIPEA, THF

Compounds 39 and 40

[0197] Compound **38** (0.382 g, 0.852 mmol) was diluted in MeCN (10 mL) and *N,N*-diisopropylethylamine (0.60 mL, 3.41 mmol) was added, followed by a solution of Compound **16** in MeCN (1.5 mL). The clear, yellow solution was allowed to age at room temperature for 4h and the volatiles were removed *in vacuo*. The residue was taken up in a 3/1 $CHCl_3$/IPA (v/v, 13 mL) and treated with saturated Na_2CO_3 (3 mL). The resulting suspension was diluted with H_2O (3 mL), and the aqueous phase thoroughly extracted with 3/1 $CHCl_3$/IPA. The combined organic layers were dried over a 3/2 (w/w) mixture of anhydrous Na_2SO_4/anhydrous Na_2CO_3 and concentrated *in vacuo*. Chromatography on SiO_2 (0-20% MeOH/CH_2Cl_2) afforded 0.043 g (14%) of Compound **39** as a colorless film (LC/MS *m/z*: 362.1 $(M+H)^+$) and 0.105 g (34%) of Compound **40** as a colorless film (LC/MS *m/z*: 362.1 $(M+H)^+$).

Example M

[0198] A flask was charged with Compound **39** (0.048 g, 0.133 mmol) and Compound **29** was added as a 0.2 M solution in THF (0.8 mL, 0.160 mmol). THF (1 mL) was added, followed by DIPEA (0.026 mL, 0.145 mmol), HOBt (0.022 g, 0.160 mmol) and finally EDC (0.028 mL, 0.160 mmol). The clear, colorless solution was allowed to age overnight. Volatiles were removed *in vacuo* and the residue chromatographed on SiO_2 (0-20% MeOH/CH_2Cl_2). Fractions containing the desired compound were concentrated *in vacuo* and submitted to preparatory LC/MS purification to afford 0.018 g (20%) of Example **M** as a colorless film LC/MS *m/z*: 657.2 $(M+H)^+$; ^{1}H-NMR (CDCl3, 300 MHz) δ 8.95 (s, 1H); 7.88 (br s, 1H); 7.27-7.04 (m, 5H); 7.04 (s, 1H); 6.60-6.20 (m, 2H); 5.22 (m, 2H); 5.12 (d, *J* = 9.3 Hz, 1H); 4.50 (m, 2H); 4.01 (br s, 1H); 3.83 (m, 2H); 3.38 (m, 1H); 3.10-2.94 (m, 3H); 2.74 (m, 2H); 2.23 (m, 1H); 1.64-1.15 (m, 8H); 1.40 (d, *J* = 6.9Hz, 6H); 0.96 (m, 6H); 0.83 (t, *J* = 6.9 Hz, 3H).

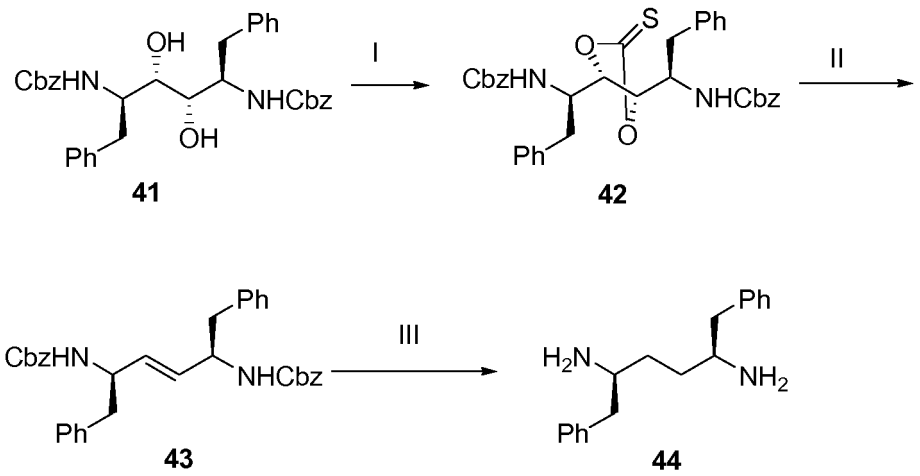
Example N

[0199] Example **N** was prepared using procedures similar to those used to prepare Example **M,** using the following reagents: Compound **40** (0.055 g, 0.152 mmol); Compound **29** (0.92 mL of 0.2 M THF solution, 0.183 mmol); THF (1 mL); DIPEA (0.040 mL, 0.228 mmol); HOBt (0.025 g, 0.182 mmol); EDC (0.032 mL, 0.182 mmol). 0.087 g (87%) of Example **N** was isolated as a colorless film (LC/MS *m/z*: 657.2 $(M+H)^+$; ^{1}H-NMR CDCl3, 300 MHz) δ 8.84 (s, 1H); 7.86 (s, 1H); 7.27-7.04 (m, 5H); 7.04 (s, 1H); 6.28 (br s, 1H); 6.12 (br s, 1H); 5.25 (m, 2H); 5.11 (d, *J* = 9.0 Hz, 1H); 4.62-4.32 (m, 2H); 4.19 (m, 1H); 4.01 (br s, 1H); 3.53 (m, 1H); 3.10-2.90 (m, 3H); 2.72 (d, *J* = 6.0 Hz, 2H); 2.29 (m, 1H); 1.65-1.18 (m, 8H); 1.39 (d, *J* = 6.9 Hz, 6H); 1.00-0.78 (m, 9H).

Preparation of Examples O and P

[0200]

Scheme 16



I. TCDI/THF/65 °C; II. $P(OEt)_3$/160 °C; III. H_2, 10% Pd/C.

Compound 41

[0201] Compound **41** was prepared following the procedure described in J. Org. Chem. 1996, 61, 444-450.

Compound 42

[0202] A mixture of Compound **41** (1.73 g, 3 mmol) and 1,1'-thiocarbonyldiimidazole (1.14 g, 6.1 mmol) in THF (60 mL) was heated at 65 °C for 72 hours. Solvent was removed under reduced pressure. The mixture was diluted with EtOAc, and washed successively with 1N HCl, water, and brine, and dried over $MgSO_4$. Purification by flash column chromatography (silica gel, hexanes/EtOAc = 1/1) gave Compound **42** (980 mg). m/z: 611.1 $(M+H)^+$.

Compound 43

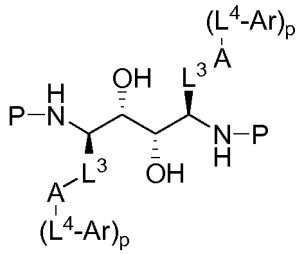
[0203] A mixture of Compound **42** (980 mg) and triethyl phosphite (10 mL) was heated at 160 °C for 14 hours. The excess reagents were removed under reduced pressure. Recrystallization from a mixture of hexanes (11 mL) and EtOAc (3.6 mL) gave Compound **57** (580 mg). m/z: 557.3 $(M+Na)^+$.

Compound 44

[0204] A mixture of Compound **43** (580 mg) in i-PrOH/EtOAc (12 mL/12 mL) was hydrogenated under high pressure (100 psi) for 24 hours in the presence of 10%Pd/C (200 mg). Celite was added and the mixture was stirred for 5 minutes. Filtration and evaporation gave Compound **44** (285 mg). m/z: 269.1 $(M+H)^+$.

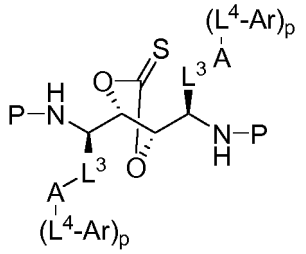
[0205] The skilled practitioner will recognize that the procedure outlined in Scheme **16** can be used to prepare a variety

of 1,4-substituted 1,4-diamines analogous to Compound **44.** For example, an amine-protected 2,3-dihydroxy-1,4-diamine analogous to Compound **41** can be prepared:



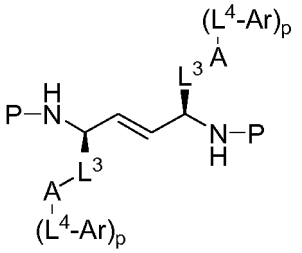
Analogs of Compound **41**

wherein L^3, A, Ar, and P are as defined herein, and protecting group "P" is any amine protecting group described in described in Protective Groups in Organic Synthesis, Theodora W. Greene and Peter G. M. Wuts (John Wiley & Sons, Inc., New York, 1999, ISBN 0-471-16019-9). The analogs of Compound **41** can then be transformed, according to the methods outlined in Scheme **16,** to form analogs of Compound **42:**



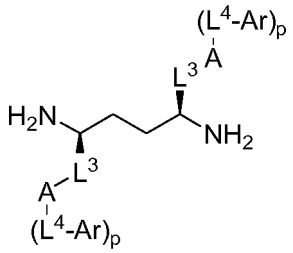
Analogs of Compound **42;**

analogs of Compound **43:**



Analogs of Compound **43;**

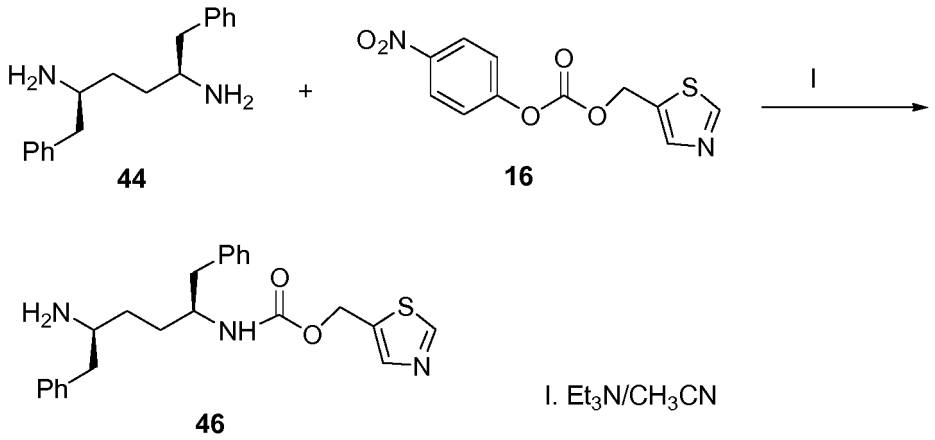
and analogs of Compound **44:**



Analogs of Compound **44.**

[0206] It will also be recognized that stereochemical configurations other than those shown (i.e., enantiomers or diasteriomers) can be prepared by the selection of analogs of Compound **41** having the appropriate stereochemical configuration at the chiral centers.

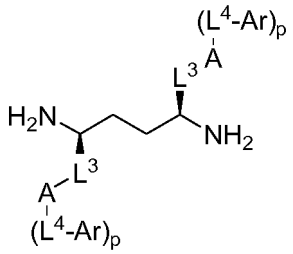
Scheme 17



Compound 46

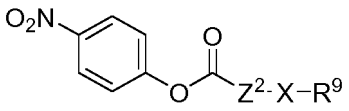
[0207] To the solution of Compound **45** (950 mg, 3.5 mmol) in CH_3CN (36 mL) at 0 °C was added Compound **16** (892 mg, 3.2 mmol), followed by diisopropylethylamine (1.2 mL, 7 mmol). The mixture was stirred for 12 hours at 25 °C. The mixture was diluted with EtOAc, and washed successively with saturated Na_2CO_3, water, and brine. Purification by flash column chromatography (silica gel, 100% EtOAc to CH_2Cl_2/MeOH = 4/1) gave Compound **46** (770 mg). m/z: 410.1 $(M+H)^+$.

[0208] The skilled practitioner will recognize that the procedure outlined in Scheme **17** can be used to prepare a variety of compounds analogous to Compound **46.** For example, 1,4-diamines analogous to Compound **44** can be prepared as discussed above:



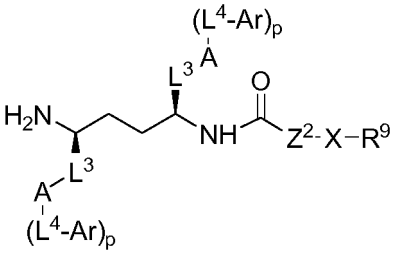
Analogs of Compound **44.**

[0209] The analogs of Compound **44** can then be reacted with analogs of Compound **16:**



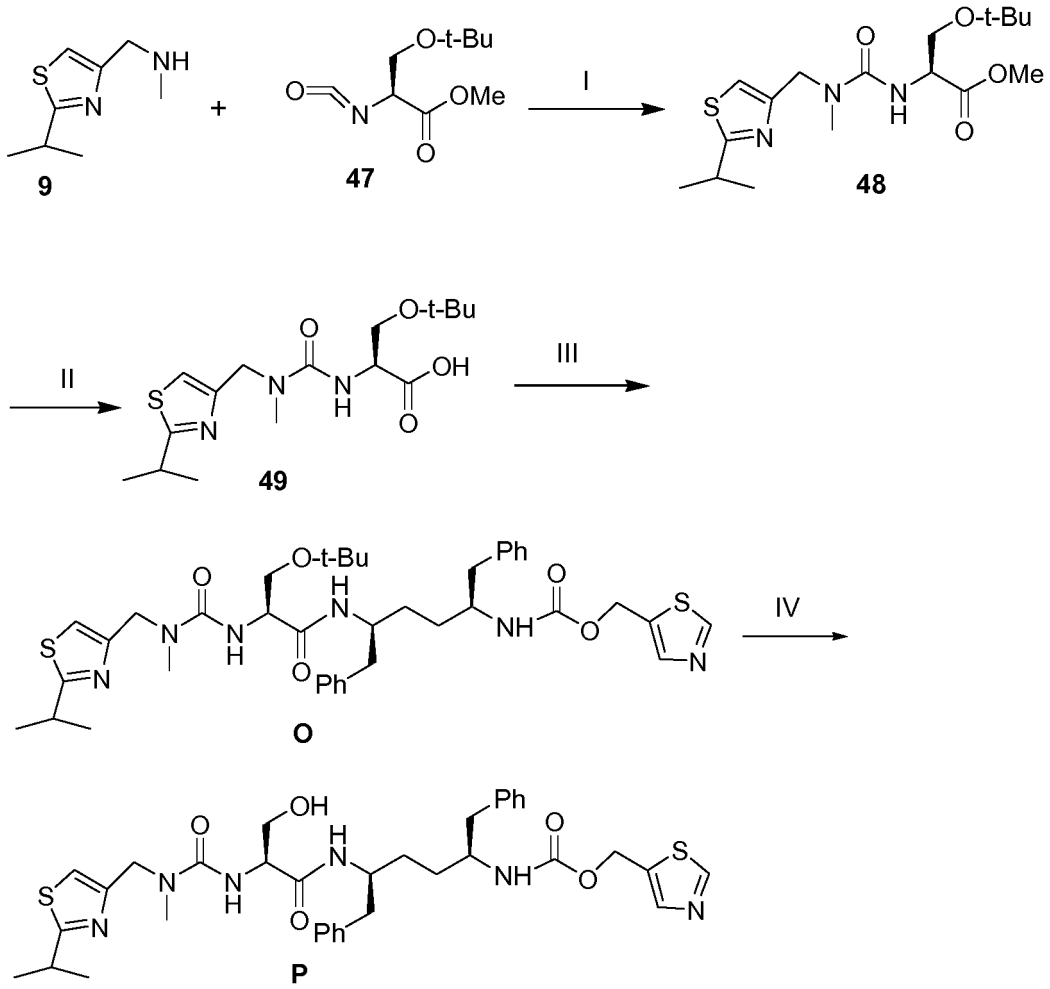
Analogs of Compound **16**,

(wherein Z^2, X, and R^9 are as defined herein) to form analogs of Compound **46:**



[0210] It will also be recognized that stereochemical configurations other than those shown (i.e., enantiomers or diasteriomers) can be prepared by the selection of analogs of Compound **44** having the appropriate stereochemical configuration at the chiral centers.

Scheme 18



I. CH_2Cl_2/25 °C; II. a. NaOH/dioxane/H_2O; b. HCl; III. amine 46/EDC/HOBt; IV. a. TFA; b. NaOH

Compound 47

[0211] Compound **47** is commercially available from TCI.

Compound 48

[0212] To a solution of Compound **9** (500 mg, 3 mmol) in CH_2Cl_2 (3 mL) was added Compound **47** (500 mg, 2.5 mmol). The mixture was stirred for 14 hours. Purification by flash column chromatography (hexanes/EtOAc = 1/1.5) gave Compound **48** (242 mg). m/z: 372.1 $(M+H)^+$.

Compound 49

[0213] To a solution of Compound **48** (240 mg, 0.65 mmol) in dioxane (4 mL) and water (4 mL) was added sodium hydroxide (40 mg, 1 mmol). The mixture was stirred for 1 hour and acidified with 4 N HCl in dioxane (0.25 mL, 1 mmol). The mixture was extracted with EtOAc and organic phase was dried with $MgSO_4$. Concentration gave Compound **49** (200 mg). m/z: 356.2 $(M-H)^+$.

Example O

[0214] To a solution of corresponding acid **49** (30 mg, 0.08 mmol) and Compound **46** (22 mg, 0.05 mmol) in THF (1

mL) were added HOBt (15 mg, 0.11 mmol), EDC (20 μL, 0.11 mmol), and disopropylethylamine (0.2 mL). The mixture was stirred for 12 hours and concentrated. Purification by flash column chromatography (hexanes/EtOAc = 1/5 to 0/100) gave Example **O** (17 mg). m/z: 749.3 $(M+H)^+$.

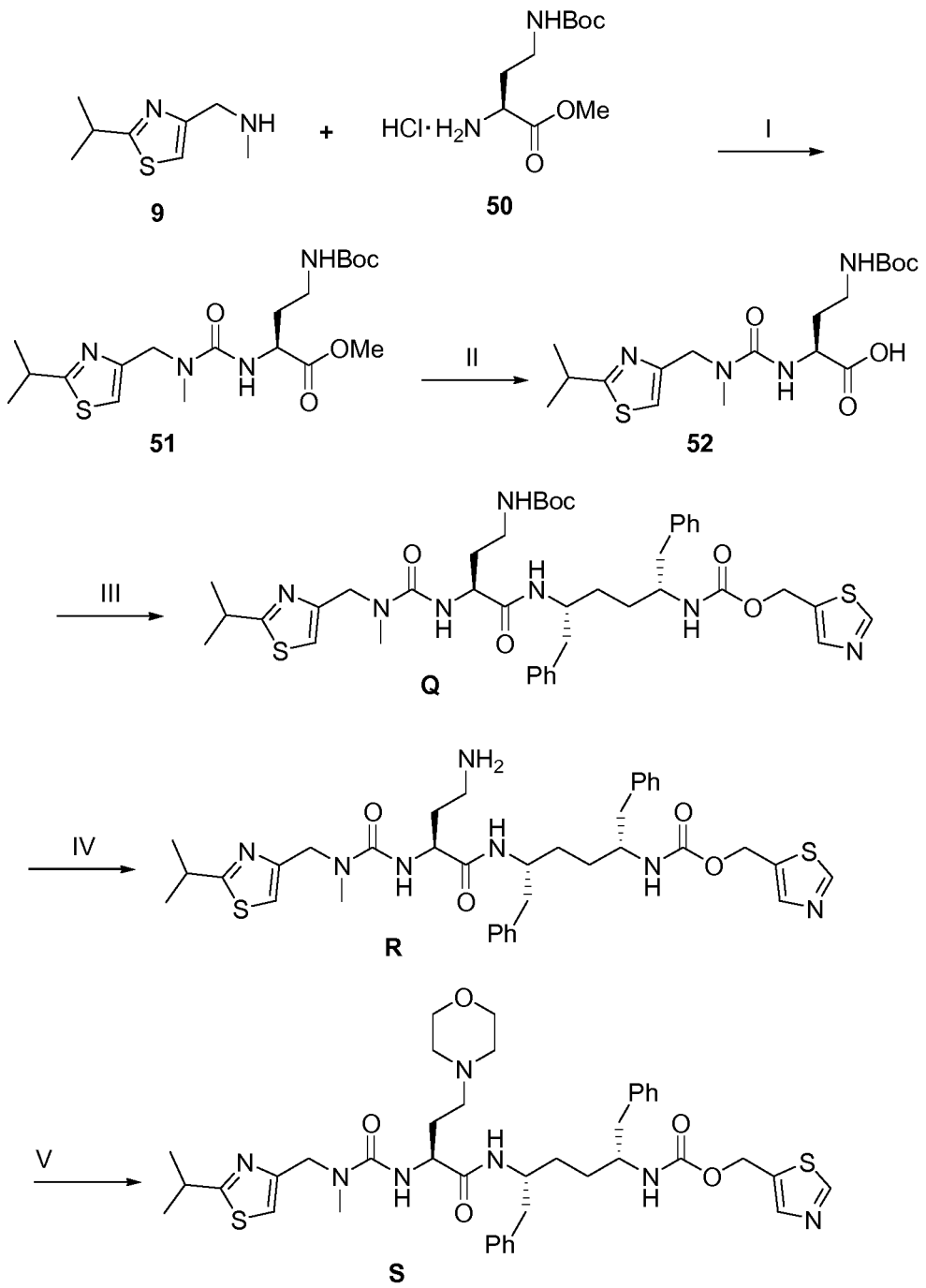
Example P

[0215] To Example **O** (17 mg) was added TFA (2 mL). The mixture was stirred for 3 hours and concentrated. The mixture was diluted with THF (2 mL) and 1.0 N NaOH solution was added until pH 11. The mixture was stirred for 10 minutes, and extracted with EtOAc. The organic phase was washed with water and brine. Purification by flash column chromatography (EtOAc) gave Example **P** (12 mg). ^{1}H-NMR ($CDCl_3$) b 8.76 (1 H, s), 7.79 (1 H, s), 7.25-6.9 (11 H, m), 6.51 (1 H, broad), 5.42 (1 H, m), 5.18 (2 H, m), 4.42 (2 H, m), 4.22 (1 H, m), 4.10 (1 H, m), 3.95 (1 H, m), 3.79 (1 H, m), 3.58 (1 H, m), 3.23 (1 H, m), 2.93 (3 H, s), 2.9-2.5 (4 H, m), 1.6-1.2 (10 H, m); m/z: 693.2 $(M+H)^+$.

Preparation of Examples O, R, and S

[0216]

Scheme 19



I. CDI, DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd. 8, DIPEA, EDC, HOBt, THF;
IV.a. HCl/dioxane; b. Na_2CO_3; V.
$(BrCH_2CH_2)_2O$, $NaHCO_3$, DMF

Compound 50

[0217] Compound **50** is commercially available from Chem Impex International, and used without further purification.

Compound 51

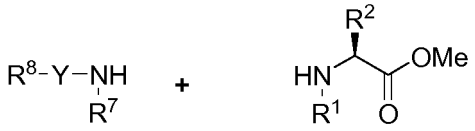
[0218] Compound **50** (7.0 g, 26.0 mmol) was dissolved in CH_2Cl_2 (330 mL) and 1,1-carbonyldiimidazole (4.22 g, 26.0

mmol) was added, followed by i-Pr_2NEt (19 mL, 104 mmol). The solution was stirred at 25 °C for 12 hours. Compound **9** (4.44 g, 26.0 mmol) was dissolved in 20 mL of CH_2Cl_2 and added to the reaction mixture. The solution was stirred at 25 °C for 7 hours. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate and washed with water and brine. The organic layers were dried (Na_2SO_4), filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 66-100% EtOAc/Hexane gradient) gave Compound **51** (7.34 g). m/z: 429.0 $(M+H)^+$.

Compound 52

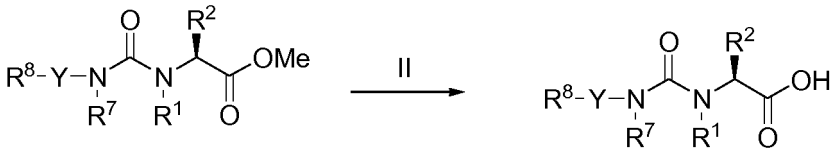
[0219] Compound **51** (7.34 g, 17.13 mmol) was dissolved in THF (90 mL) and 1M aqueous LiOH (35 mL) was added. The mixture was stirred at 25 °C for 0.5 hour. The reaction was quenched with 1M HCl (51 mL) and the mixture was adjusted to pH 2. The mixture was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered, and evaporated to provide Compound **52** (7.00 g). The recovered Compound **52** was used in the next step without further purification. m/z: 415.0 $(M+H)^+$.

[0220] The skilled practitioner will recognize that the procedure outlined in Scheme **19** can be used to prepare a variety of compounds analogous to Compounds **51** and **52.** For example, amines analogous to Compound **9** can be reacted with the appropriate amino ester analogous to Compound **50:**



Cmpd **9** Analog Cmpd **50** Analog ,

to form compounds analogous to Compound **51,** which are further reacted to form compounds analogous to Compound **52:**



Cmpd **51** Analogs Cmpd **52** Analogs ;

wherein R^1, R^2, R^7, R^8 and Y are as defined herein.

[0221] It will also be recognized that stereochemical configurations other than those shown (i.e., enantiomers or diasteriomers) can be prepared by the selection of analogs of Compound **50** having the appropriate stereochemical configuration at the chiral center.

Example Q

[0222] Compound **52** (2.57 g, 6.21 mmol) was dissolved in THF (67 mL). Compound **8** (2.10 g, 5.13 mmol) was added, followed by HOBt (1.04 g, 7.70 mmol), i-Pr_2NEt (3.67 mL, 20.52 mmol), and EDC (1.82 mL, 10.26 mmol). The mixture was stirred at 25 °C for 12 hours. The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 5% iPrOH/CH_2Cl_2) gave Example **Q** (3.02 g). m/z: 806.2 $(M+H)^+$.

Example R

[0223] Example **Q** (3.02 g, 3.74 mmol) was suspended in 4.0 N HCl/dioxane solution (30 mL) and stirred at 25 °C for 3 hours. Solvent was removed under reduced pressure and Et_2O was poured into the reaction mixture. The resulting suspension was stirred vigorously for 1.5 hours. The solid was allowed to settle and the ether layer was decanted. Washing of the precipitate with Et_2O was repeated two more times. The product was dried *in vacuo* to afford a white

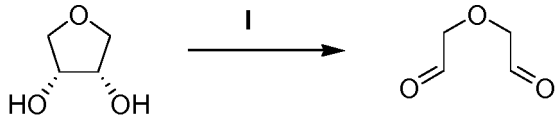
solid (3.18 g, quantitative yield). Saturated aqueous Na_2CO_3 solution was added to above solid (3.18 g) with stirring until solid disappeared. The aqueous solution was extracted with ethyl acetate. The organic phases were dried over Na_2SO_4, filtered, and evaporated to afford Example **R** as a yellow foam (2.44g, 81%). The recovered Example **R** was used without further purification in the next step. m/z: 706.1 $(M+H)^+$.

Example S

Method I:

[0224] Example **R** (1.00g, 1.42 mmol) was dissolved in DMF (20 mL) and bromoethyl ether (196 μL, 1.56 mmol) was added dropwise, followed by $NaHCO_3$ (0.239 g, 2.84 mmol). The reaction mixture was stirred at 25 °C for 2 hours. The solution was heated to 65 °C and stirred for 12 hours. The solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed sequentially with water and brine. The organic phase was dried over Na_2SO_4 filtered, and evaporated. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 5-95% CH_3CN/water) gave Compound **70** (580 mg, 53%). ^1H NMR ($CDCl_3$) b 8.98 (s, 1H); 7.90 (s, 1H); 7.75 (m, 1H); 7.40-7.00 (m, 11H), 6.55 (br s, 1H); 5.58 (m, 1H); 5.28, 5.19 (d_{AB}, J=14 Hz, 2H); 4.70-4.37 (m, 3H); 3.99 (m, 5H); 3.76 (br s, 1H); 3.65-3.30 (m, 3H); 2.97 (m, 5H); 2.90-2.60 (m, 6H); 2.28 (br s, 1H); 1.91 (br s, 1H); 1.60-1.30 (m, 10H). m/z: 776.2 $(M+H)^+$ Method II:

Scheme 20



53 **54**

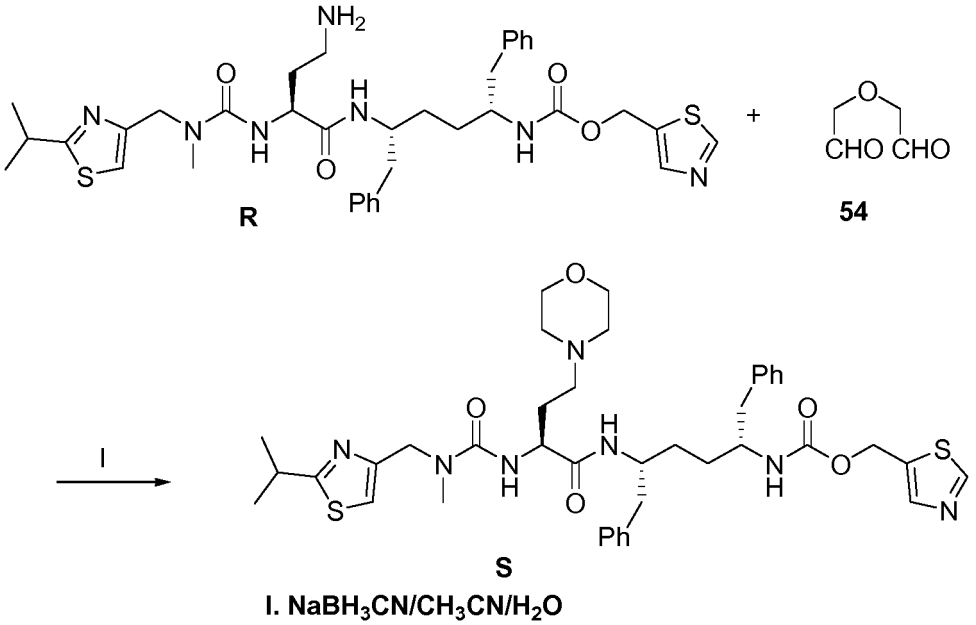
I. $NaIO_4$, H_2O

Compound 54

[0225] Compound **54** was prepared following the procedure described in J. Med. Chem. 1993, 36, 1384 (herein incorporated by reference in its entirety for all purposes).

[0226] To solution of Compound **53** (0.550 g, 5.28 mmol) (Sigma-Aldrich) in H_2O (8.8 mL) at 0 °C was added $NaIO_4$ (1.016 g, 4.75 mmol). The mixture was allowed to slowly warm to 25 °C and stirred for 12 hours. Solid $NaHCO_3$ was added to the reaction mixture until pH 7. $CHCl_3$ (16 mL) was added and the mixture was allowed to stir for 5 minutes. The mixture was filtered and the solid was washed with $CHCl_3$ (6 mL). The combined $H_2O/CHCl_3$ solution was used directly in the next step without further purification.

Scheme 21



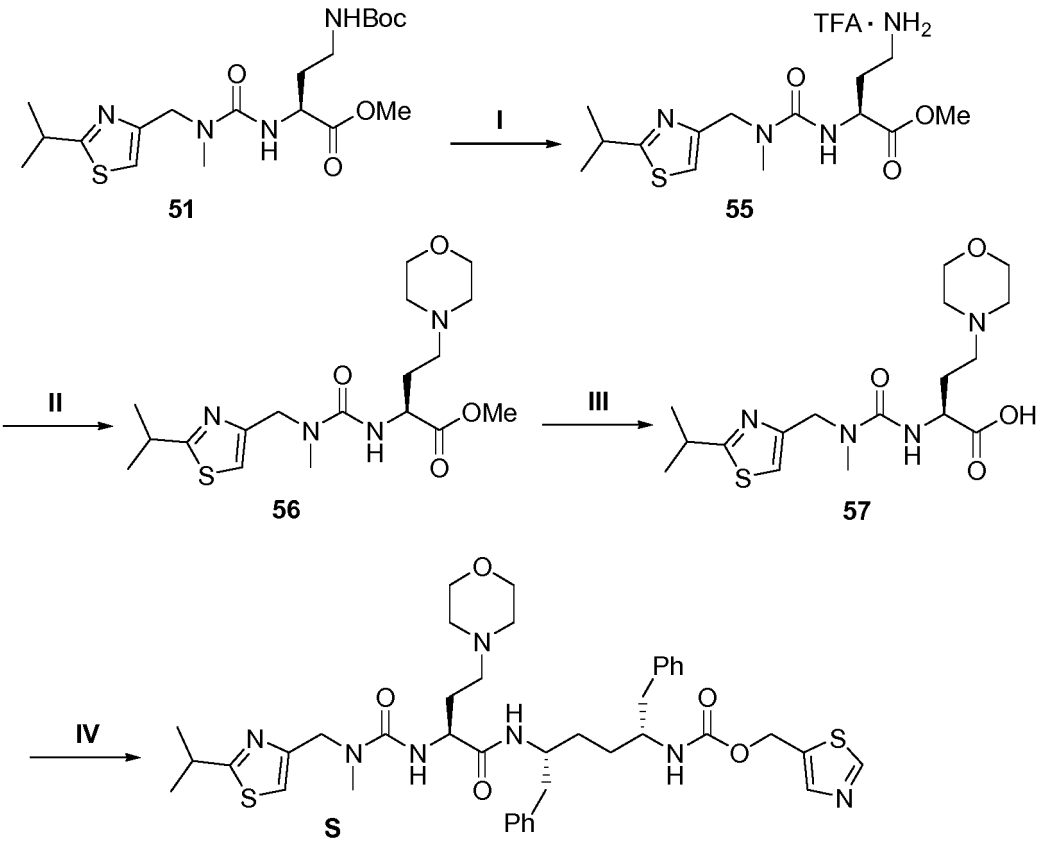
Example S

[0227] To a solution of Example **R** (70 mg, 0.1 mmol) in CH_3CN (5 mL) was added sodium cyanoborohydride (50 mg) in water (5 mL). To the above mixture was added a solution of dialdehyde Compound **54** (0.6 mmol) in $CHCl_3/H_2O$) (4 mL/ 1 mL). The mixture was stirred for 12 hours, and basified with saturated Na_2CO_3 solution. The mixture was extracted with EtOAc, and organic phase was washed with water and brine, and dried over Na_2SO_4. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column) gave Example **S** (57 mg).

Method III

[0228]

Scheme 22



I. TFA, CH_2Cl_2; II. Cmpd 54, $NaBH_3CN$, H_2O/CH_3CN; III. LiOH, THF/H_2O; IV. amine Cmpd 8, DIPEA, EDC, HOBt, THF

Compound 55

[0229] Compound **51** (0.28 g, 0.66 mmol) was dissolved in CH_2Cl_2 (4 mL) and TFA (1 mL) was added dropwise. The reaction was allowed to stir at 25 °C for 1 hour. The solvent was removed under reduced pressure to afford Compound **55** (0.39 g). m/z: 329.0 $(M+H)^+$.

Compound 56

[0230] To a solution of Compound 55 (0.39 g, 0.89 mmol) in CH_3CN (45 mL) was added $NaBH_3CN$ (0.45 g, 7.12 mmol) and H_2O (45 mL). A solution of Compound **54** (0.55 g, 5.34 mmol) in $CHCl_3/H_2O$ (40 mL) was added. The mixture was stirred at 25 °C for 12 hours. The reaction mixture was made basic with saturated aqueous Na_2CO_3 and extracted sequentially with ethyl acetate and dichloromethane. The combined organic layers were washed sequentially with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 0-10% MeOH/CH_2Cl_2 gradient) gave Compound **56** (0.17 g). m/z: 399.1 $(M+H)^+$.

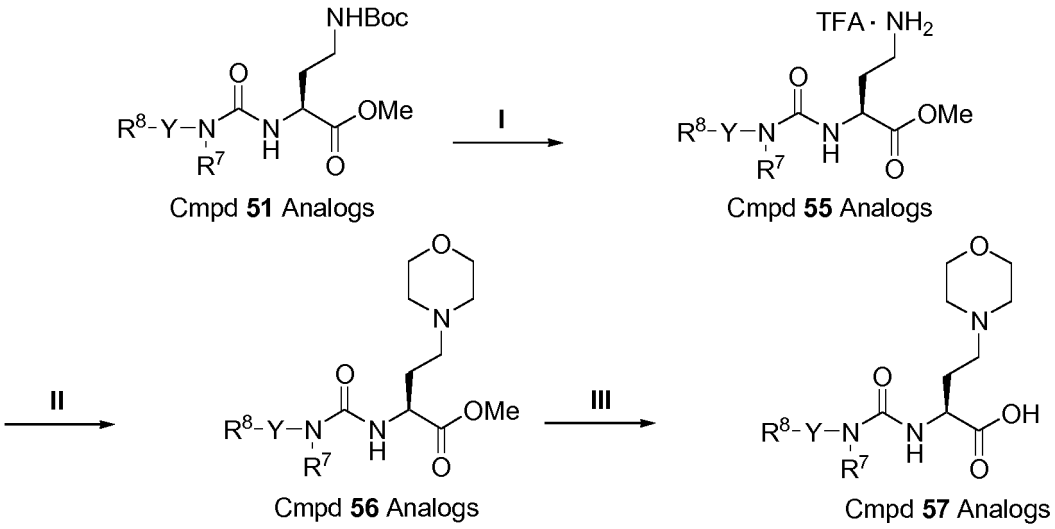
Compound 57

[0231] Compound **56** (377 mg, 0.95 mmol) was dissolved in THF (4 mL) and 1M aqueous LiOH (1.90 mL) was added. The mixture was stirred at 25 °C for 1 hour. The reaction was neutralized with 1M HCl. THF was removed under reduced pressure and the aqueous solution was lyophilized to afford Compound **57** (365 mg). The material was used directly in the next step without further purification. m/z: 385.1 $(M+H)^+$.

Example S

[0232] Example **S** (185 mg, 57%) was prepared following the same procedure as for Example **Q**, except that Compound **57** (160 mg, 0.42 mmol) was used instead of Compound **52.** mass m/z: 776.2 $(M+H)^+$.

[0233] The skilled practitioner will recognize that the procedure outlined in Scheme **22** can be used to prepare a variety of compounds analogous to Compounds **55-57:**



I. TFA, CH_2Cl_2; II. Ex. R, $NaBH_3CN$, H_2O/CH_3CN; III. LiOH, THF/H_2O

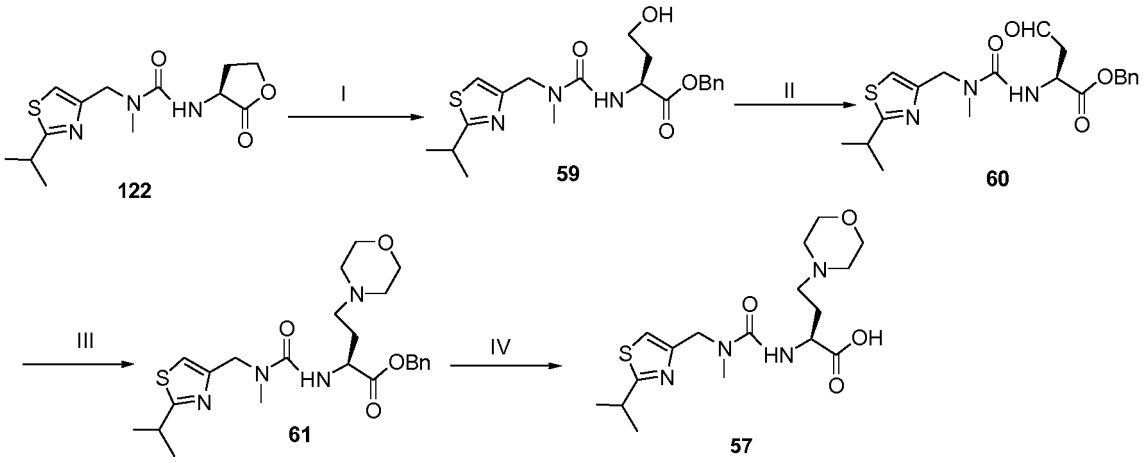
wherei
n R^7, R^8 and Y are as defined herein.

[0234] It will also be recognized that stereochemical configurations other than those shown (i.e., enantiomers or diasteriomers) can be prepared by the selection of analogs of Compound **51** having the appropriate stereochemical configuration at the chiral center.

Method IV

[0235]

Scheme 23



I. a. NaOH/H2O; b. BnBr; II. SO3/pyridine; III. morpholine/NaBH(OAc)3; IV. a. NaOH; b. HCl

Compound 59

[0236] To a solution of Compound **122** (33 g, 112 mmol) (see Scheme **69**) in ethanol (366 mL) at 0 ºC was added a solution of sodium hydroxide (4.7 g, 117 mmol) in water (62 mL). The mixture was stirred for one hour at 25 ºC, and solvents were removed under reduced pressure. The mixture was coevaporated with ethanol (3x400 mL), and dried at 60 ºC for two hours under high vacuum to give a white solid. To the solution of above solid in DMF (180 mL) was added benzyl bromide (16.2 mL, 136 mmol). The mixture was stirred for 16 hours under darkness, and was quenched with water (300 mL). The mixture was extracted with EtOAc (4x300 mL). The combined organic phase was washed with water (5x) and brine, and dried over Na_2SO_4. Concentration gave Compound **59** (48 g), which was used in the next step without further purification.

Compound 60

[0237] A mixture of Compound **59** (33 g, 74 mmol) in DMSO (225 mL) and Et_3N (36 mL) was stirred for 30 minutes. The mixture was cooled to 0-10ºC, SO_3-pyridine (45 g) was added, and the stirring was continued for 60 minutes. Ice (300 g) was added, and the mixture was stirred for 30 minutes. EtOAc (300 mL) was added and sat. Na_2CO_3 was added until pH was 9-10. The organic phase was separated from the aqueous phase, and the aqueous phase was extracted with EtOAc (2x300ml). The combined organic phases were washed with sat Na_2CO_3 (2x), water (3x), and brine. The mixture was dried over Na_2SO_4 and concentrated to give Compound **60** (32 g), which was used directly in next step without further purification.

Compound 61

[0238] To a solution of Compound **60** (32 g) in CH_3CN (325 mL) was added morpholine (12.9 mL, 148 mmol), with a water bath around the reaction vessel, followed by HOAc (8.9 mL, 148 mmol), and $NaBH(OAc)_3$ (47 g, 222 mmol). The mixture was stirred for 12 hours. CH_3CN was removed under reduced pressure, and the mixture was diluted with EtOAc (300 mL). Sat. Na_2CO_3 was added until the pH was 9-10. The organic phase was separated from the aqueous phase, and the aqueous phase was extracted with EtOAc (2x300 mL). The combined organic phases were washed with sat Na_2CO_3 (2x), water (1x), and brine (1x). The mixture was dried over Na_2SO_4. The resulting residue was concentrated and purified by silica gel column chromatography (EtOAc to DCM/iPrOH =10/1) to give Compound **61** (30 g).

Compound 57

[0239] To a solution of Compound **61** (26.5 g, 56 mmol) in ethanol (160 mL) at 0ºC was added a solution of sodium hydroxide (2.5 g, 62 mmol) in water (30 mL). The mixture was stirred for one hour at 25ºC, and solvents were removed under reduced pressure. The mixture was diluted with water (200 mL), and was washed with CH_2Cl_2 (6x100 mL). The

water phase was acidified with 12 N HCl (5.2 mL), and was dried under reduced pressure to give Compound **57** (22 g).

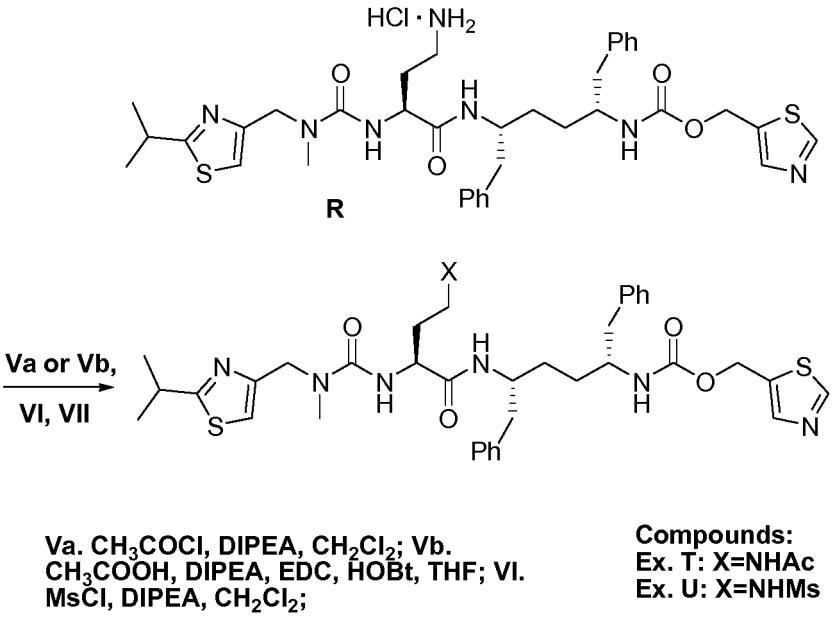
Example S

[0240] Compound **57** was converted to Example **S** using the procedure described in Method III, above.

Preparation of Compounds T and U

[0241]

Scheme 24



Example T

Method I

[0242] The hydrochloride salt of Example **R** (100 mg, 0.13 mmol) was suspended in CH_2Cl_2 (2 mL) and dissolved by addition of iPr_2NEt (69 μL). Acetyl chloride (11 μL) was added dropwise and the mixture was allowed to stir at 25 °C for 4 hours. The solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (stationary phase: silica gel; eluent: 8% iPrOH/CH_2Cl_2) gave Example **T** (39 mg, 40%). m/z: 748.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) b 8.85 (s, 1H); 7.87 (s, 1H); 7.73 (s, 1H); 7.40-7.00 (m, 13H); 6.45 (br s, 1H); 5.70 (m, 1H); 5.32, 5.22 (d_{AB}, *J*=13 Hz, 2H); 4.51 (s, 2H); 4.20-3.90 (m, 4H); 3.78 (m, 1H); 3.38 (m, 2H); 3.20-2.50 (m, 8H); 1.95 (s, 4H); 1.82 (m, 2H); 1.41 (m, 6H).

Method II

[0243] Saturated aqueous Na_2CO_3 solution was added to the hydrochloride salt of Example **R** (3.18 g, 3.46 mmol) while stirring until the solid disappeared. The aqueous solution was extracted with ethyl acetate. The organic phases were dried over Na_2SO_4, filtered, and evaporated to afford Example **R** as a yellow foam (2.44g, 81%). This material was used without further purification in the next step. m/z: 706.1 $(M+H)^+$.

[0244] Example **R** (300 mg, 0.43 mmol) was dissolved in THF (5.5 mL). Acetic acid (37 μL, 0.64 mmol) was added, followed by HOBt (85 mg, 0.64 mmol), iPr_2NEt (304 μL, 1.70 mmol), and EDC (151 μL, 0.85 mmol). The reaction mixture was allowed to stir at 25 °C for 12 hours. The solvent was removed under reduced pressure. The residue was diluted with EtOAc and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 10% MeOH/CH_2Cl_2) gave Example **T** (249 mg, 77%). m/z: 748.2 $(M+H)^+$.

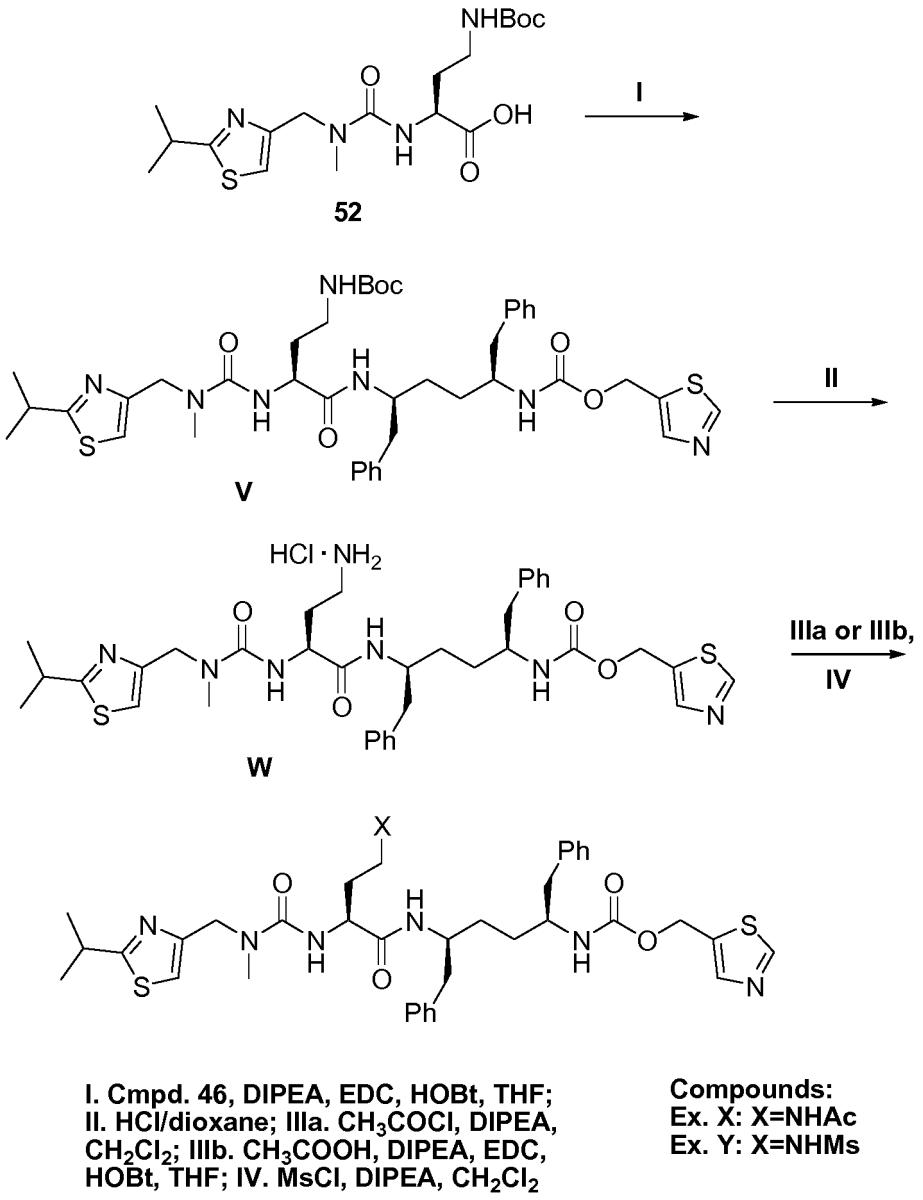
Example U

[0245] Example **R** (100 mg, 0.13 mmol) was suspended in CH_2Cl_2 (2 mL) and dissolved by addition of iPr_2NEt (69 μL). Methanesulfonyl chloride (12 μL) was added dropwise and the mixture was allowed to stir at 25 °C for 4 hours. The solvent was removed *in vacuo*. Purification of the residue by flash column chromatography (stationary phase: silica gel; eluent: 8% iPrOH/CH_2Cl_2) gave Example **U** (55 mg, 54%). m/z: 784.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.90 (s, 1H); 7.88 (s, 1H); 7.40-7.00 (m, 12H); 6.54 (br s, 1H); 6.19 (br s, 1H); 5.25 (s, 2H); 4.53 (s, 2H); 4.38 (m, 1H); 4.12 (m, 1H); 3.79 (m, 1H); 3.79 (m, 1H); 3.48 (m, 1H); 2.99 (s, 3H); 2.90 (m, 3H); 2.73 (m, 6H); 2.00 (m, 1H); 1.79 (m, 1H); 1.60-1.18 (m, 10H).

Preparation of Examples V, W, X and Y

[0246]

Scheme 25



I. Cmpd. 46, DIPEA, EDC, HOBt, THF; II. HCl/dioxane; IIIa. CH_3COCl, DIPEA, CH_2Cl_2; IIIb. CH_3COOH, DIPEA, EDC, HOBt, THF; IV. MsCl, DIPEA, CH_2Cl_2

Compounds:
Ex. X: X=NHAc
Ex. Y: X=NHMs

Example V

[0247] Example **V** (692 mg) was prepared following the same procedure used for preparing Example **Q**, except that Compound **46** was used instead of Compound 8. m/z: 806.2 $(M+H)^+$.

Example W

[0248] Example **W** (770 mg, quantitative yield) was prepared following the same procedure for Example **R** except that Example V was used instead of Example **Q**. m/z: 706.2 $(M+H)^+$. ^1H NMR (CD_3OD) b 9.86 (s, 1H); 8.23 (s, 1H); 7.66 (s, 1H); 7.40-7.00 (m, 10H); 5.29, 5.17 (d_{AB}, *J*=13 Hz, 2H); 4.80-4.60 (m, 2H); 4.18 (s, 2H); 4.26 (m, 2H); 3.67 (br s, 1H); 3.55 (m, 2H); 3.03 (m, 3H); 2.90-2.60 (m, 8H); 2.53 (s, 2H); 2.00-1.80 (m, 2H); 1.85-1.30 (m, 10H).

Compound 59

Method I

[0249] Example **X** (107 mg, 55%) was prepared following the Method I procedure for Example **T** except that Example **W** was used instead of Example **R.** m/z: 748.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) b 8.80 (s, 1H); 7.85 (s, 1H); 7.40 (m, 1H); 7.38-7.00 (m, 10H), 6.94 (s, 1H); 6.30 (m, 2H); 5.75 (m, 1H); 5.30, 5.23 (d_{AB}, J=13 Hz, 2H); 4.54, 4.46 (d_{AB}, *J*=8 Hz, 2H); 4.20-3.90 (m, 2H); 3.74 (br s, 1H); 3.46 (br s, 1H); 3.28 (m, 1H); 2.98 (s, 3H); 2.83 (m, 3H); 2.72 (m, 1H); 2.62 (m, 1H); 2.05-1.20 (m, 15H).

Method II

[0250] Example **X** (205 mg, 65%) was prepared following the Method II procedure for Example **T** except that Example **W** was used instead of Example **R.** m/z: 748.2 $(M+H)^+$.

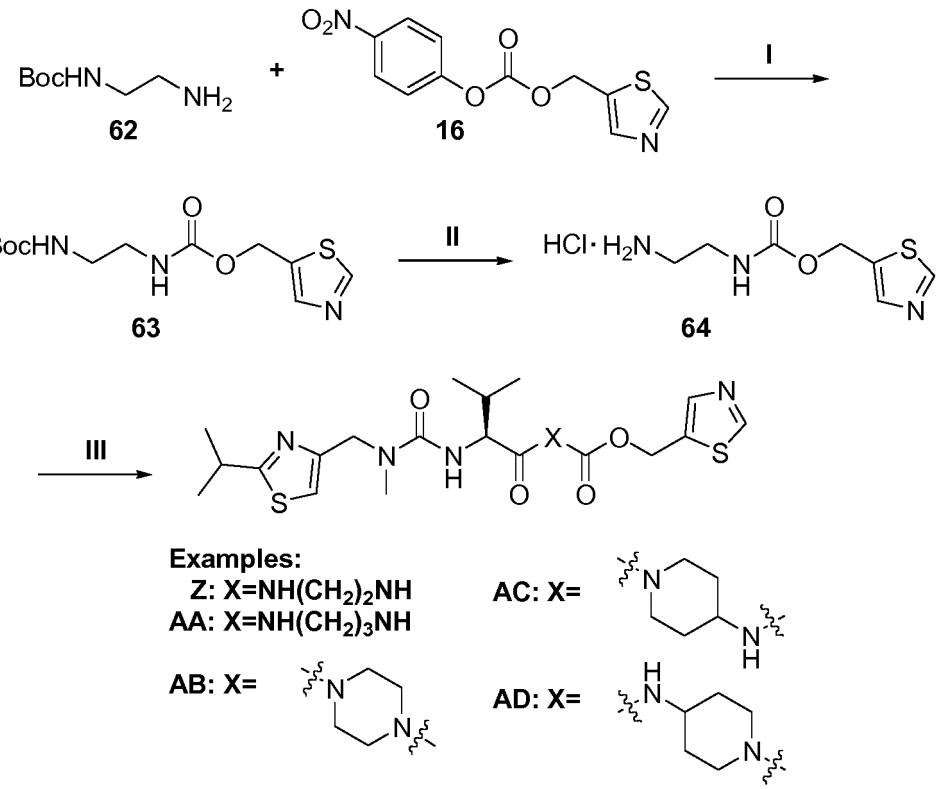
Example Y

[0251] Example **Y** (106 mg, 50%) was prepared following the same procedure for Example U, except that Example **W** was used instead of Example **R.** m/z: 784.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) b 8.81 (s, 1H); 7.85 (s, 1H); 7.40-7.05 (m, 10H), 6.98 (s, 1H); 6.22 (br s, 1H); 5.78 (s, 1H); 5.25 (m, 4H); 4.29 (m, 2H); 4.33 (br s, 1H); 4.12 (br s, 1H); 3.77 (br s, 1H); 3.10 (br s, 1H); 2.98 (s, 3H); 2.90 (s, 3H); 2.73 (m, 6H); 2.00-1.20 (m, 12H).

Preparation of Examples Z-AD

[0252]

Scheme 26



I. DIPEA, CH_3CN; II. HCl/dioxane, EtOAc; III. acid 29, DIPEA, EDC, HOBt, THF

Compound 62

[0253] Tert-butyl 2-aminoethylcarbamate **(62)** is commercially available from Aldrich, and was used without further purification.

Compound 63

[0254] To a solution of Compound **62** (2.0 mmol) in CH_3CN (15 mL) was added Compound **16** (1.82 mmol), followed by the addition of *N,N*-diisopropylethylamine (0.61 mL). The mixture was stirred at 25 °C for 12 hours. The solvent was removed *in vacuo*, and the residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic layers were dried with Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 25-100% EtOAc/hexane gradient) gave Compound **63.** m/z: 301.9 $(M+H)^+$.

Compound 64

[0255] To a solution of Compound **63** (1.05 mmol) in EtOAc (3 mL) was added 4N HCl/dioxane solution (1.1 mL). The mixture was allowed to stir at 25 °C for 12 hours. The solvent was removed under reduced pressure, and Compound 64 was obtained as a white powder. This material was used in the next step without further purification. m/z: 216.0 $(M+H)^+$.

Example Z

[0256] Compound **64** (70 mg, 0.29 mmol) was dissolved in THF (2.2 mL). Compound **29** (91 mg, 0.29 mmol) was added to the reaction flask as a 1.0M solution in THF, followed by HOBt (59 mg, 0.44 mmol), *N,N*-diisopropylethylamine (207 μL, 1.16 mmol), and EDC (103 μL, 0.58 mmol). The reaction was allowed to stir for 12 hours at 25 °C and concentrated under reduced pressure. The residue was diluted with EtOAc and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic layers were dried with Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 0-10% MeOH/CH_2Cl_2 gradient) gave Example **Z** (54 mg, 38%). m/z: 497.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.78 (s, 1H); 7.83 (s, 1H); 6.99 (s, 1H); 6.80 (br s, 1H); 6.22 (br s, 1H); 5.87 (br

s, 1H); 5.25 (s, 2H); 4.43 (s, 2H); 3.97 (m, 1H); 3.34 (m, 4H); 2.95 (s, 3H); 2.22 (m, 2H); 1.38 (d, *J*=7 Hz, 6H); 0.97 (d, *J*=7 Hz, 6H).

Example AA

[0257] Example **AA** was prepared following the procedures for steps **I-III (Scheme 20)** for Example **Z,** with the exception that tert-butyl 3-aminopropylcarbamate was used instead of tert-butyl 2-aminoethylcarbamate (Compound **62).** After Combiflash® purification, 38 mg (34%) of Example **AA** was obtained. m/z: 511.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.78 (s, 1H); 7.84 (s, 1H); 6.96 (s, 2H); 6.17 (br s, 1H); 5.80 (m, 1H); 5.26 (m, 2H); 4.44 (s, 2H); 4.09 (m, 1H); 3.40-3.10 (m, 5H); 2.97 (s, 3H); 2.20 (m, 1H); 1.60 (m, 2H); 1.36 (d, *J*=7 Hz, 6H); 0.96 (d, *J*=7 Hz, 6H).

Example AB

[0258] Example **AB** was prepared following the procedures for steps **I-III (Scheme 20)** for Example **Z,** with the exception that tert-butyl 1-piperazinecarboxylate was used instead of tert-butyl 2-aminoethylcarbamate (Compound **62**). After Combiflash® purification, 64 mg (45%) of Example **AB** was obtained. m/z: 523.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) b 8.82 (s, 1H); 7.89 (s, 1H); 6.96 (s, 1H); 5.93 (br s, 1H); 5.35 (s, 2H); 4.62 (m, 1H); 4.50 (m, 2H); 3.80-3.40 (m, 8H); 3.34 (m, 1H); 3.00 (s, 3H); 1.97 (m, 1H); 1.40 (d, *J*=7 Hz, 6H); 0.96, 0.93 (d, *J*=7 Hz, 6H).

Example AC

[0259] Example **AC** was prepared following the procedures for steps I-III **(Scheme 20)** for Example **Z,** with the exception that tert-butyl 4-amino-1-piperidinecarboxylate was used instead of tert-butyl 2-aminoethylcarbamate (Compound **62).** After Combiflash® purification, 60 mg (44%) of Example **AC** was obtained. m/z: 537.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.82 (s, 1H); 7.87 (s, 1H); 6.97 (s, 1H); 5.82 (br s, 1H); 5.30 (m, 3H); 4.80-4.40 (m, 5H); 4.03 (m, 1H); 3.72 (br s, 1H); 3.34 (m, 1H); 3.18 (m, 1H); 3.01 (s, 3H); 2.79 (m, 1H); 2.20-1.90 (m, 4H); 1.40 (d, *J*=7 Hz, 6H); 0.97, 0.90 (d, *J*=7 Hz, 6H).

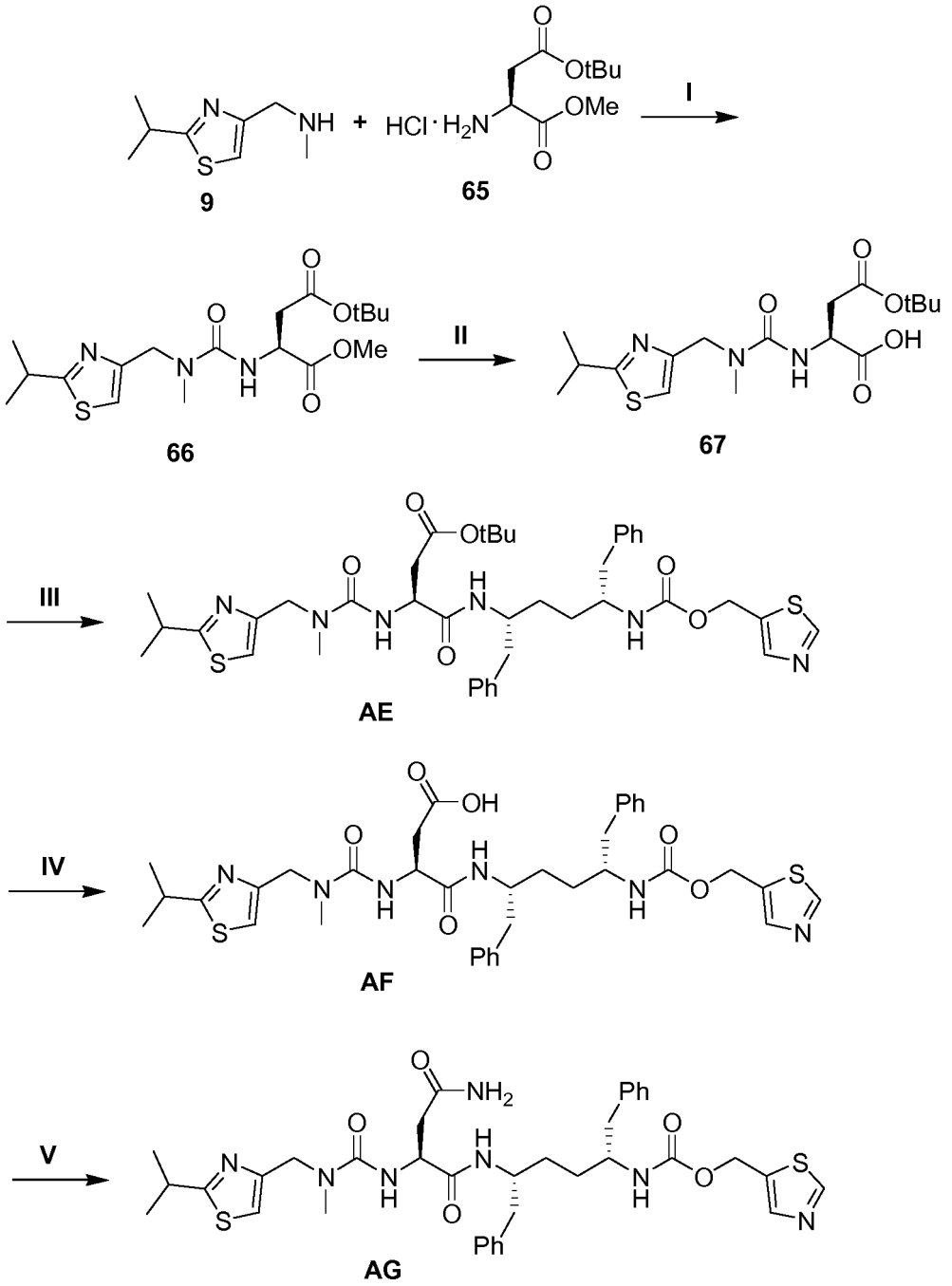
Example AD

[0260] Example **AD** was prepared following the procedures I-III for Example **Z,** with the exception that tert-butyl 4-piperidinylcarbamate was used instead of tert-butyl 2-aminoethylcarbamate (Compound **62).** After Combiflash® purification, 49 mg (36%) of Example **AD** was obtained. m/z: 537.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) b 8.82 (s, 1H); 7.87 (s, 1H); 7.01 (s, 1H); 6.33 (br s, 1H); 6.11 (br s, 1H); 5.32 (s, 2H); 4.47 (s, 2H); 4.20-3.80 (m, 4H); 3.35 (m, 1H); 3.10-2.80 (m, 6H); 2.21 (m, 2H); 1.90 (m, 2H); 1.40 (d, *J*=7 Hz, 6H); 0.97 (d, *J*=7 Hz, 6H).

Preparation of Examples AE-AG

[0261]

Scheme 27



I. CDI, DIPEA, CH_2Cl_2; II. NaOH, THF/H_2O; III. Cmpd. 8, DIPEA, EDC, HOBt, THF; IV. neat TFA; V. $(Boc)_2O$, NH_4HCO_3, pyridine, dioxane, DMF

Compound 65

[0262] Compound **65** is commercially available from Chem Impex International, and was used without further purification.

Compound 66

[0263] Compound **65** (956 mg, 4.0 mmol) was dissolved in CH_2Cl_2 (45 mL) and 1,1-carbonyldiimidiazole (648 mg,

4.0 mmol) was added, followed by i-Pr_2NEt (2.8 mL, 16 mmol). The solution was stirred at 25 °C for 12 hours. Compound **9** (679 mg, 4.0 mmol) was dissolved in CH_2Cl_2 (5 mL) and added to the reaction. The mixture was allowed to stir for 5 hours. Then, the solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and filtered through celite. The ethyl acetate was then removed *in vacuo*. Purification by flash column chromatography (stationary phase: silica gel; eluent: EtOAc) gave Compound **66** (841 mg). m/z: 400.0 $(M+H)^+$.

Compound 67

[0264] Compound **66** (841 mg, 2.11 mmol) was dissolved in THF (9 mL) and 2N aqueous NaOH was added. The solution was stirred at 25 °C for 2 hours. The reaction was adjusted to pH 2 with 1N HCl. The mixture was extracted with ethyl acetate, dried over Na_2SO_4, filtered, and evaporated. Compound **67** (772 mg) was used directly in the next step without further purification. m/z: 386.0 $(M+H)^+$.

Example AE

[0265] Compound **67** (569 mg, 1.48 mmol) was dissolved in THF (17 mL). Compound **8** (970 mg, 2.37 mmol) was added, followed by HOBt (300 mg, 2.22 mmol), i-Pr_2NEt (1.06 mL, 5.92 mmol), and EDC (0.52 mL, 2.96 mmol). The mixture was stirred at 25 °C for 36 hours. The solvent was removed under reduced pressure. The resulting residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 8% iPrOH/CH_2Cl_2) gave Example **AE** (3.02 g). m/z: 777.2 $(M+H)^+$.

Example AF

[0266] Example **AE** (100 mg, 0.13 mmol) was dissolved in neat TFA (3 mL). The mixture was stirred at 25 °C for 2 hours. The solvent was removed under reduced pressure. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 5-95% CH_3CN/H_2O gradient) gave Example **AF** (20 mg, 21%). m/z: 721.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.92 (s, 1H); 7.91 (s, 1H); 7.40-7.00 (m, 11H); 6.41 (br s, 1H); 6.12 (br s, 1H); 5.40-5.00 (m, 3H); 4.70-4.50 (m, 3H); 4.05 (br s, 1H); 3.81 (br s, 1H); 3.51 (br s, 1H); 2.97 (s, 3H); 2.90-2.60 (m, 6H); 1.41 (d, *J*=7 Hz, 10H).

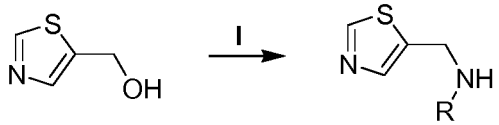
Example AG

[0267] Example **AF** (70 mg, 0.10 mmol) was dissolved in dioxane (0.5 mL). DMF (83 μL), pyridine (25 μL, 0.29 mmol), di-*tert*-butyldicarbonate (27 mg, 0.13 mmol), and ammonium bicarbonate (15 mg, 0.19 mmol) were added. The mixture was stirred at 25 °C for 48 hours, then diluted with ethyl acetate and washed sequentially with water and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by reverse-phase HPLC (Phenomenex Synergi® Comb-HTS column, eluent: 5-95% CH_3CN/H_2O gradient) gave Example **AG** (35 mg, 50%). ^1H NMR ($CDCl_3$) b 8.80 (s, 1H); 7.84 (s, 1H); 7.40-7.00 (m, 10H); 7.08 (s, 1H); 6.83 (m, 1H); 6.65 (m, 1H); 5.40-5.10 (m, 4H); 4.60-4.40 (m, 3H); 4.06 (m, 1H); 3.79 (m, 1H); 3.36 (m, 1H); 2.97 (s, 3H); 2.90-2.60 (m, 6H); 2.45 (m, 1H); 1.70-1.20 (m, 10H).

Preparation of Compounds 68 and 69

[0268]

Scheme 28



15

68: R=methyl
69: R=cyclopropyl

I. a. MsCl, TEA, CH_3CN; b. $MeNH_2/H_2O$; c. cyclopropyl amine

Compound 15

[0269] Compound 15 is commercially available from Molekula, and was used without further purification.

Compound 68

[0270] Compound **15** (6.81 g, 59.1 mmol) was dissolved in CH_3CN (340 mL) and methanesulfonyl chloride (7.03 mL, 65.1 mmol) was added, followed by triethylamine (9.03 mL, 65.1 mmol). After the mixture was stirred for 20 min, 40% wt. methylamine/water (516 mL) was added to the reaction mixture. The solution was stirred for 12 hours at 25 °C. Solvent was removed under reduced pressure and the residue was partitioned between saturated aqueous Na_2CO_3 and CH_2Cl_2. The organic phase was separated, dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (stationary phase: silica gel; eluent: 0-10% MeOH/CH_2Cl_2 gradient) gave Compound **68** (5.07 g). m/z: 128.9 $(M+H)^+$.

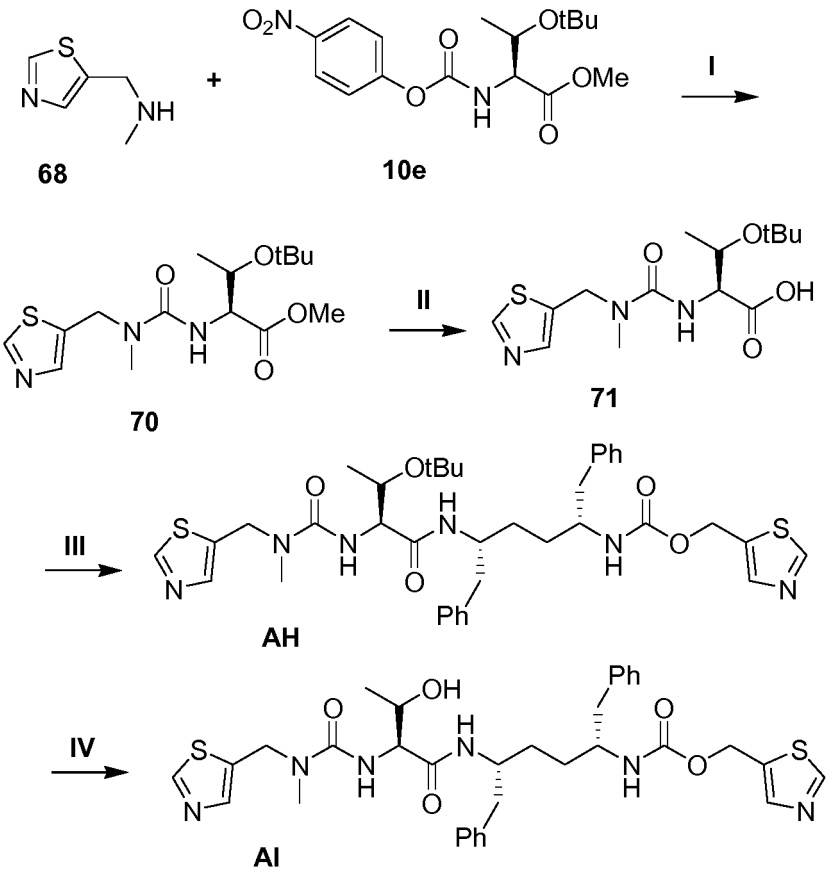
Compound 69

[0271] Compound **15** (10.0 g, 80 mmol) was dissolved in CH_3CN (500 mL) and methanesulfonyl chloride (7.0 mL, 88 mmol) was added, followed by triethylamine (12.3 mL, 88 mmol). After the mixture was stirred for 2h, cyclopropylamine (140 mL, 2000 mmol) in CH_3CN (500 mL) was added to the reaction mixture. The solution was stirred for 36 hours at 25 °C. Solvent was removed under reduced pressure and the slurry was partitioned between saturated aqueous Na_2CO_3 and 3:1 CH_2Cl_2:i-PrOH. The organic phase was separated, dried over Na_2SO_4, filtered, and evaporated. Compound **69** (12.81 g) was used in the next step without further purification. m/z: 155.0 $(M+H)^+$.

Preparation of Examples AH and AI

[0272]

Scheme 29



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd. 8, HOBt, EDC, DIPEA, THF;
IV. a. neat TFA; b. NaOH, THF, H_2O

Compound 70

[0273] Compound **68** (1.00 g, 7.80 mmol) was dissolved in THF (25 mL) and Compound **10e** (2.51 g, 7.09 mmol) was added, followed by *N,N*-dimethaminopyridine (200 mg, 1.63 mmol), and triethylamine (4.34 mL, 31.2 mmol). The mixture was allowed to stir at 60 °C for 6 hours. Solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, H_2O, and brine. The organic layer was dried over Na_2SO_4, filtered, and evaporated. The resulting residue was purified by Combiflash® (stationary phase: silica gel; eluent: 20-100% EtOAc/Hexane gradient) to give Compound **70** (2.14 g). m/z: 343.9 $(M+H)^+$.

Compound 71

[0274] Compound **70** (2.14 g, 6.23 mmol) was dissolved in THF (25 mL) and 1M aqueous LiOH (12.5 mL) was added. The mixture was stirred at 25°C for 2 hours. The reaction was quenched with 1M HCl (15 mL) and the mixture was adjusted to pH 2. The mixture was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered, and evaporated to provide Compound **71** (1.96 g). This material was used in the next step without further purification. m/z: 330.0 $(M+H)^+$.

Example AH

[0275] Compound **71** (43 mg, 0.13 mmol) was dissolved in THF (1.5 mL). Compound **8** (50 mg, 0.12 mmol) was added, followed by HOBt (24 mg, 0.18 mmol), iPr_2NEt (86 μL, 0.48 mmol), and EDC (42 μL, 0.24 mmol). The mixture was stirred at 25°C for 12 hours. The solvent was removed under reduced pressure, and the resulting residue was diluted with ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 1-10% MeOH/CH_2Cl_2 gradient) gave Example **AH** (66 mg). m/z: 721.2 $(M+H)^+$.

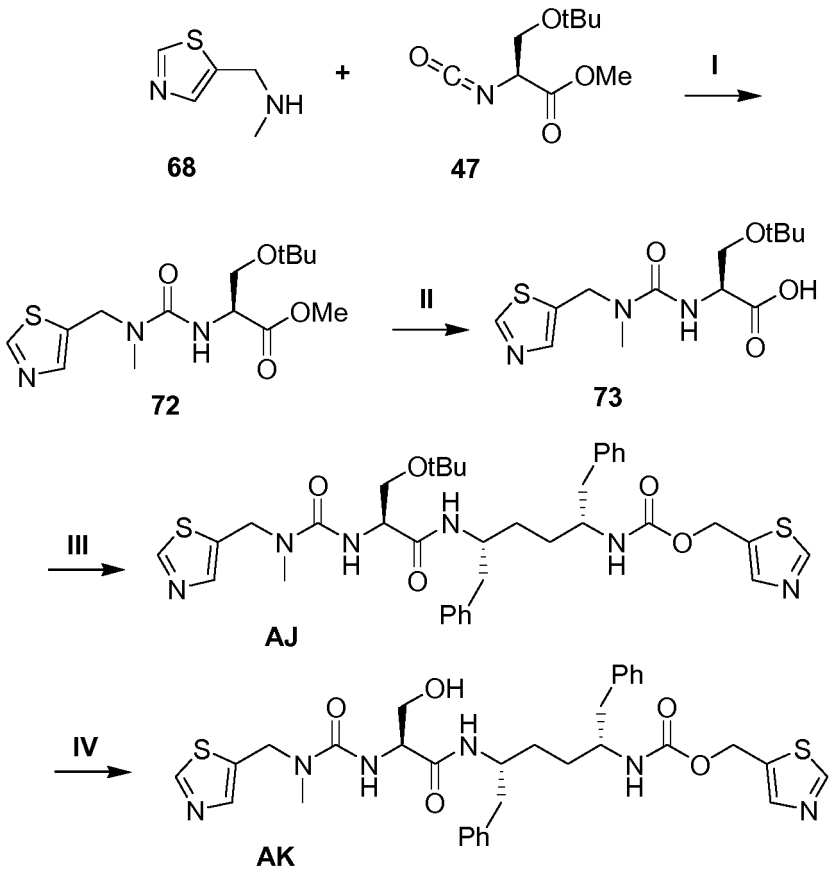
Compound AI

[0276] Example **AH** (66 mg, 0.09 mmol) was dissolved in TFA and allowed to stir at 25 °C for 3 hours. The solvent was removed under reduced pressure and the residue was diluted with THF (3 mL) and 2N aqueous NaOH was added until pH 12. The mixture was allowed to stir for 20 min and extracted with EtOAc. The organic layer was washed sequentially with water and brine, dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (stationary phase: silica gel; eluent: 0-20% i-PrOH/CH_2Cl_2 gradient) gave Example **AI** (71 mg, 97%). m/z: 665.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.84 (s, 1H); 8.80 (s, 1H); 7.85 (s, 1H); 7.79 (s, 1H); 7.40-7.00 (m, 10H); 6.69 (m, 1H); 5.34 (m, 1H); 5.24 (s, 2H); 4.86 (m, 2H); 4.73, 4.59 (d_{AB}, J=16 Hz, 2H); 4.30 (s, 1H); 4.15 (m, 2H); 3.86 (br s, 1H); 2.88 (s, 3H); 2.85-2.60 (m, 4H); 2.01 (s, 1H); 1.58 (s, 2H); 1.44 (s, 2H); 1.09 (d, J= 6 Hz, 3H).

Preparation of Examples AT and AK

[0277]

Scheme 30



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd. 8, HOBt, EDC, DIPEA, THF;
IV. a. neat TFA; b. NaOH, THF, H_2O

Compound 47

[0278] Compound **47** is commercially available from TCI America, and was used without further purification.

Compound 72

[0279] Compound **72** was prepared following procedure for Compound **48** (Method II), except that Compound **68** was used instead of Compound **9.**

Compound 73

[0280] Compound **73** was prepared following procedure for Compound **49,** except that Compound **72** was used instead of Compound **48.**

Example AJ

[0281] Example **AJ** (70 mg) was prepared following the same procedure used to prepare Example **AH,** with the exception that Compound **73** (41 mg, 0.13 mmol) was used instead of Compound **71.** m/z: 707.2 $(M+H)^+$.

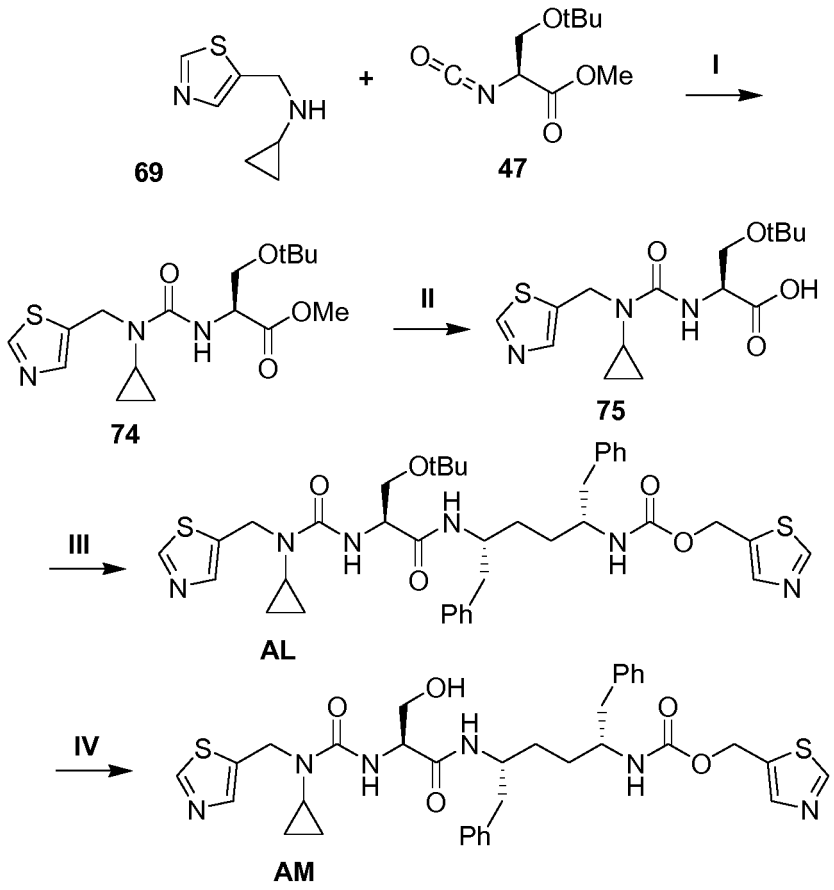
Example AK

[0282] Example **AK** (43 mg, 67%) was prepared following the same procedure used to prepare Example **AI,** with the exception that Example **AJ** (70 g, 0.10 mmol) was used instead of Example **AH.** m/z: 651.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) b 8.83 (s, 2H); 7.84 (s, 1H); 7.79 (s, 1H); 7.40-7.00 (m, 10H); 6.65 (br s, 1H); 5.47 (br s, 1H); 5.24 (s, 2H); 4.90 (m, 1H); 4.82-4.50 (m, 2H); 4.30-4.00 (m, 3H); 3.84 (br s, 1H); 3.49 (m, 1H); 2.87 (s, 3H); 2.75 (br s, 5H); 1.60-1.20 (m, 4H).

Preparation of Examples AL and AM

[0283]

Scheme 31



Compound 74

[0284] Compound **69** (1.56 g, 10.1 mmol) was dissolved in CH_2Cl_2 (10 mL). Compound **47** (1.7 g, 8.5 mmol) in CH_2Cl_2 (20 mL) was added, followed by iPr_2NEt (3.02 mL, 16.9 mmol). The reaction was stirred at 25 °C for 12 hours. The solvent was removed under reduced pressure. The residue was diluted with ethyl acetate and washed sequentially with water and brine, dried over Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 50-100% EtOAc/hexane gradient) gave Compound **74** (2.92 g). m/z: 356.0 $(M+H)^+$.

Compound 75

[0285] Compound **74** (0.97 mmol) was taken up in THF (3 mL) and treated with freshly prepared 1M LiOH (2 mmol) and stirred vigorously for 1 h. The reaction was quenched with 1M HCl (2.5 mmol) and extracted with EtOAc (3 X 15 mL). The combined organics were washed with brine (25 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo* to produce 0.331 g (quant) of Compound 75 as a colorless film (*m/z* 342.0 $(M+H)^+$).

Example AL

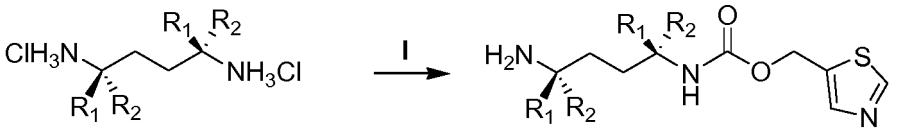
[0286] Example **AL** (2.20 g) was prepared following the same procedure used to prepare Example **AH,** with the exception that Compound **75** (2.00 g, 4.88 mmol) was used instead of Compound **71.** m/z: 733.2 $(M+H)^+$.

Example AM

[0287] Example **AM** (1.88 g, 92%) was prepared following the same procedure used to prepare Example **AI,** with the

exception that Example **AL** (2.20 g, 3.01 mmol) was used instead of Example **AH.** m/z: 677.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.79 (s, 1H); 8.72 (s, 1H); 7.82 (s, 1H); 7.77 (s, 1H); 7.40-7.00 (m, 10H); 6.59 (m, 1H); 6.31 (m, 1H); 5.23 (s, 2H); 5.00 (m, 1H); 4.72, 4.60 (d_{AB}, *J*=15 Hz, 2H); 4.18 (s, 2H); 4.03 (m, 1H); 3.84 (br s, 1H); 3.48 (m, 1H); 2.85-2.60 (m, 4H); 2.37 (br s, 2H); 1.58 (s, 2H); 1.41 (s, 2H); 0.93 (m, 2H); 0.76 (m, 2H).

Scheme 32



76: R_1 = H, R_2 = CH_3
77: R_1 = H, R_2 = CH_2CH_3

78: R_1 = H, R_2 = CH_3
79: R_1 = H, R_2 = CH_2CH_3

I. compound 16, DIPEA, MeCN

Compound 76

[0288] Compound **76** (*m*/*z* 117.0 $(M+H)^+$ of diamine) was prepared using a procedure similar to that used to prepare Compound **25** (described in Scheme **7)** except that CBZ-L-alininol was used instead of CBZ-D-phenylalininol and Step **III** was performed with 1 M HCl added.

Compound 77

[0289] Compound **77** (*m*/*z* 145.0 $(M+H)^+$ of diamine) was prepared using a procedure similar to that used to prepare Compound **76** except that (S)-(+)-2-CBZ-amino-1-butanol was used instead of CBZ-D-phenylalininol.

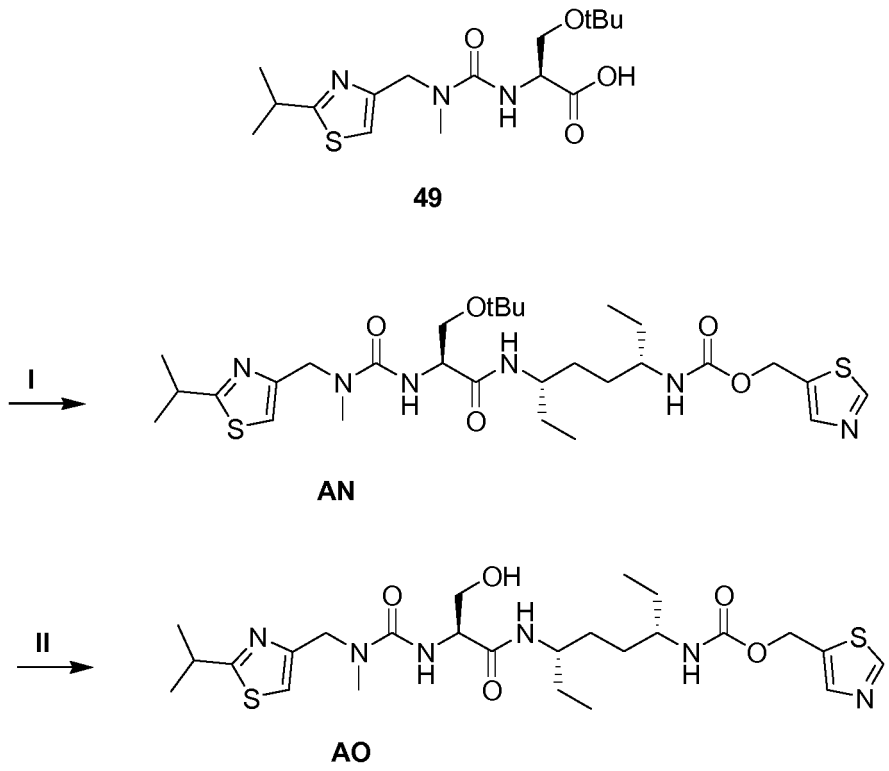
Compound 78

[0290] Compound **76** (7.93 mmol) is added to a solution of NaOH (16.7 mmol) in H_2O (5 mL) that is cooled to 0°C and diluted with MeCN (40 mL). DIPEA is added (2.1 mL, 11.9 mmol). Compound **16** (7.9 mmol) is taken up in MeCN (40 mL) and added to the reaction solution dropwise via an addition funnel over 1 h. The resulting solution is allowed to warm to room temperature overnight. The solvent is removed *in vacuo* and the residue taken up in 3/1 $CHCl_3$/IPA (50 mL). The resulting solution is washed with sat. Na_2CO_3 (50 mL) and water is added until the aqueous layer is homogeneous. The aqueous layer is extracted with 3/1 $CHCl_3$/IPA (3 X 25 mL). The combined organics are washed with saturated Na_2CO_3 (50 mL), water (50 mL) and brine (50 mL) and are dried over anhydrous Na_2SO_4. The solvent is removed *in vacuo* and the residue purified by column chromatography on SiO_2 (100% EtOAc, then 0 to 20% MeOH/DCM) to produce 0.63 g (31%) of **78** as an off-white solid. (*m*/*z* 258.0 $(M+H)^+$).

Compound 79

[0291] Compound **79** (*m*/*z* 286.1 (M+H)+) was prepared following the procedure for Compound **78** except that Compound **77** was used instead of Compound **76.**

Scheme 33



I. Cmpd. 79, HOBt, EDC, DIPEA, THF;
II. a. neat TFA; b. NaOH, THF, H_2O

Example AN

[0292] Example **AN** (68 mg) was prepared following the same procedure used to prepare Example **AH,** with the exceptions that Compound **49** (68 mg, 0.19 mmol) was used instead of Compound **71,** and Compound **79** (50 mg, 0.18 mmol) was used instead of Compound **8**. m/z: 625.2 $(M+H)^+$.

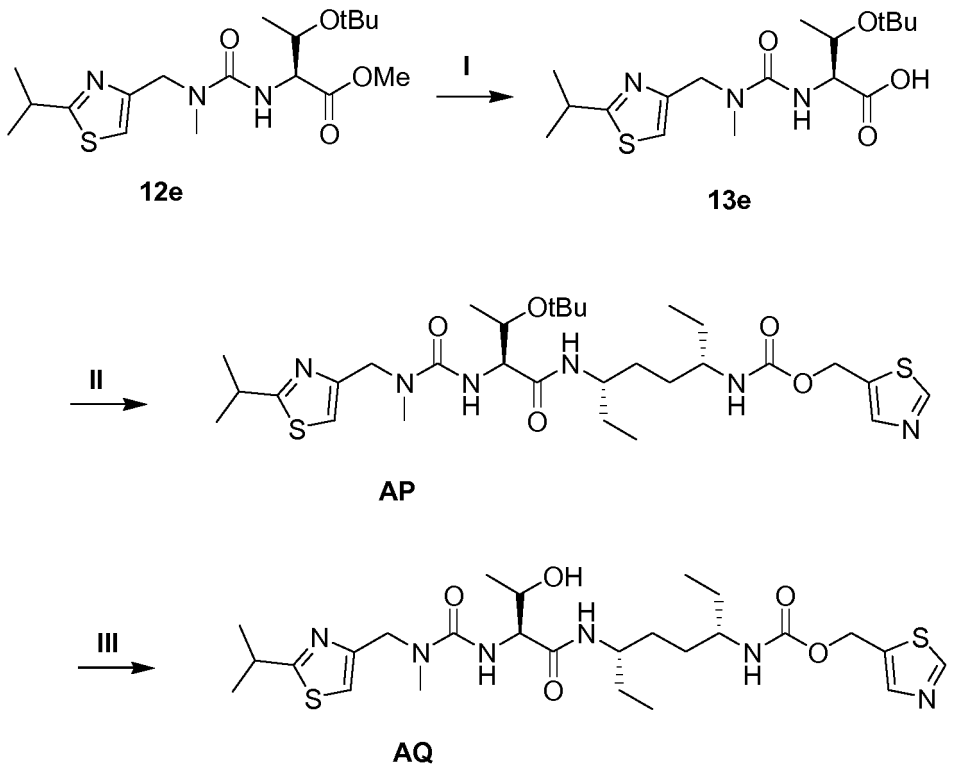
Example AO

[0293] Example **AO** (66 mg, 76%) was prepared following the same procedure used to prepare Example **AI,** with the exception that Example **AN** (43 mg, 0.13 mmol) was used instead of Example **AH.** m/z: 569.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) b 8.85 (s, 1H); 7.89 (s, 1H); 7.08 (s, 1H); 6.81 (m, 1H); 5.29 (s, 2H); 4.87 (m, 1H); 4.63, 4.48 (d_{AB}, *J*=16 Hz, 2H); 4.31 (m, 1H); 4.11 (m, 1H); 3.76 (m, 2H); 3.44 (m, 2H); 3.02 (m, 4H); 1.60-1.20 (m, 14H); 1.00-0.70 (m, 6H).

Preparation of Examples AP and AO

[0294]

Scheme 34



I. LiOH, THF/H_2O; II. Cmpd. 79, HOBt, EDC, DIPEA, THF;
III. a. neat TFA; b. NaOH, THF, H_2O

Compound 13d

[0295] Compound **13e** (1.39 g) was prepared following the same procedure used to prepare Compound **71,** with the exception that Compound **12e** (1.53 g, 3.97 mmol) was used instead of Compound **70** m/z: 372.0 $(M+H)^+$.

Example AP

[0296] Example **AP** (87 mg) was prepared following the same procedure used to prepare Example **AH,** with the exception that Compound **13e** (71 mg, 0.19 mmol) was used instead of Compound **71,** and Compound **79** (50 mg, 0.18 mmol) was used instead of Compound **8.** m/z: 639.2 $(M+H)^+$.

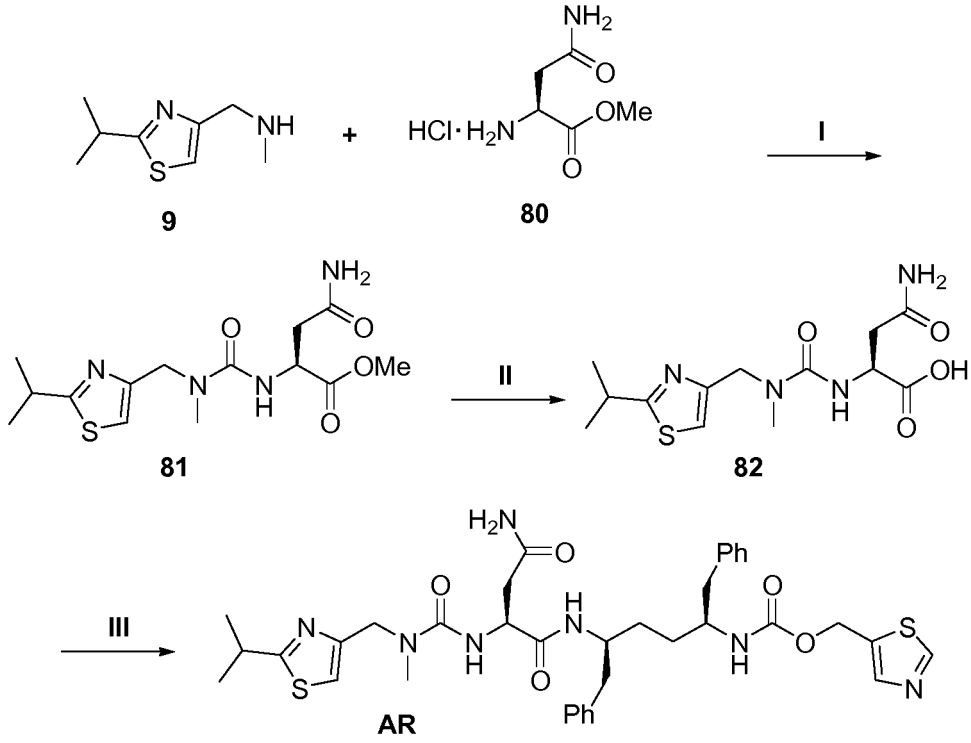
Compound AO

[0297] Example **AQ** (61 mg, 76%) was prepared following the same procedure used to prepare Example **AI,** with the exception that Example **AP** (87 mg, 0.14 mmol) was used instead of Example **AH.** m/z: 583.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.81 (s, 1H); 7.87 (s, 1H); 7.01 (s, 1H); 6.87 (m, 1H); 6.52 (s, 1H); 5.28 (m, 2H); 4.47 (m, 1H); 4.59, 4.43 (d_{AB}, J=16 Hz, 2H); 4.45 (m, 1H); 4.17 (br s, 1H); 3.75 (br s, 1H); 3.52 (br s, 1H); 3.35 (br s, 1H); 3.01 (m, 3H); 2.07 (br s, 1H); 1.60-1.10 (m, 17H); 1.00-0.70 (m, 6H).

Preparation of Example AR

[0298]

Scheme 35



I. CDI, DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd. 46, DIPEA, EDC, HOBt, THF

Compound 80

[0299] Compound **80** is commercially available from Chem Impex International, and was used without further purification.

Compound 81

[0300] Compound **80** (2.0 g, 11.0 mmol) was dissolved in CH_2Cl_2 (170 mL) and 1,1-carbonyldiimidazole (1.78 g, 11.0 mmol) was added, followed by iPr_2NEt (7.83 mL, 43.8 mmol). The solution was allowed to stir at 25°C for 12 hours. Compound **9** (1.86 g, 11.0 mmol) was dissolved in 20 mL of CH_2Cl_2 and added to the reaction mixture. The solution was stirred at 25°C for 12 hours. The solvent was removed *in vacuo* and the residue was diluted with ethyl acetate and washed water and brine. The organic layers were dried over Na_2SO_4, filtered, and evaporated. Purification by Combiflash® (stationary phase: silica gel; eluent: 66-100% EtOAc/Hexane gradient) gave Compound **81** (0.252 mg). m/z: 343.0 $(M+H)^+$.

Compound 82

[0301] Compound **82** (0.252 g, 0.74 mmol) was dissolved in THF (4 mL) and 1M aqueous LiOH (1.48 mL) was added. The mixture was stirred at 25°C for 3 hours. The reaction was quenched with 1M HCl (2 mL) and the mixture was adjusted to pH 2. The mixture was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered, and evaporated to afford Compound **82** (0.18 g). This material was used in the next step without further purification. m/z: 329.1 $(M+H)^+$.

Example AR

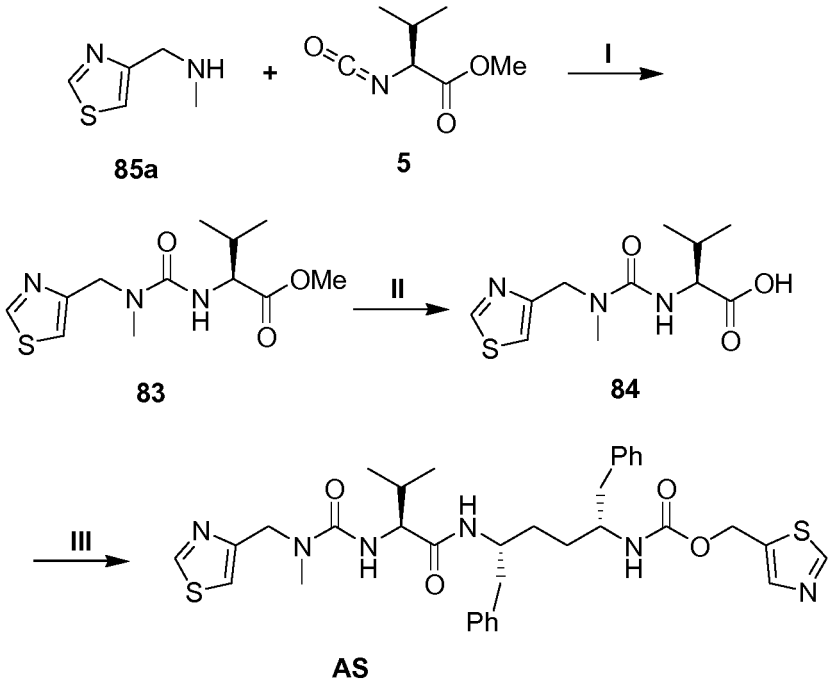
[0302] Compound **82** (182 mg, 0.55 mmol) was dissolved in THF (7.15 mL). Compound **46** (225 mg, 0.55 mmol) was added, followed by HOBt (112 mg, 0.83 mmol), iPr_2NEt (393 μL, 2.20 mmol), and EDC (194 μL, 1.10 mmol). The mixture was stirred at 25°C for 12 hours. The solvent was removed under reduced pressure. The residue was diluted ethyl

acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 5-10% MeOH/CH_2Cl_2 gradient) gave Example **AR** (208 mg, 53%). m/z: 720.2 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.80 (s, 1H); 7.84 (s, 1H); 7.40-7.00 (m, 10H); 6.97 (s, 1H); 6.83 (m, 1H); 6.65 (br s, 1H); 5.99 (m, 1H); 5.40-5.10 (m, 4H); 4.52 (m, 3H); 4.06 (m, 1H); 3.79 (m, 1H); 3.34 (m, 1H); 2.97 (s, 3H); 2.90-2.60 (m, 5H); 2.50-2.40 (br s, 1H); 1.80-1.20 (m, 10H).

Preparation of Example AS

[0303]

Scheme 36



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O; III. Cmpd. 8, HOBt, EDC, DIPEA, THF

Compound 85a

[0304] Compound **85a** was prepared following the same procedure as Compound 4, except that 4-chloromethylthiazole (purchased from TCI America) was used instead of Compound **3,** and methylamine was used instead of isopropylamine.

Compound 83

[0305] To compound **85a** (0.40 g, 3.12 mmol) in CH_2Cl_2 (9 mL) was added *N,N*-diisopropylethylamine (1.04 mL, 5.85 mmol), followed by Compound **5** (280 μL, 1.95 mmol). The reaction mixture was stirred for 3.5 hours at 25 °C. Solvent was removed under reduced pressure. Purification by Combiflash® (stationary phase: silica gel; eluent: 90-100% EtOAc/Hexane gradient) gave Compound **83** (0.51 g). m/z: 286.0 $(M+H)^+$.

Compound 84

[0306] Compound **83** (0.51 g, 1.77 mmol) was dissolved in THF (10 mL) and 1M aqueous LiOH (3.54 mL) was added. The mixture was stirred at 25°C for 2 hours. The reaction was quenched with 1M HCl (4.8 mL) and the mixture was adjusted to pH 2. The mixture was extracted with ethyl acetate. The organic layers were dried over Na_2SO_4, filtered, and evaporated to afford Compound **84** (0.430 g). This material was used in the next step without further purification. m/z: 272.0 $(M+H)^+$.

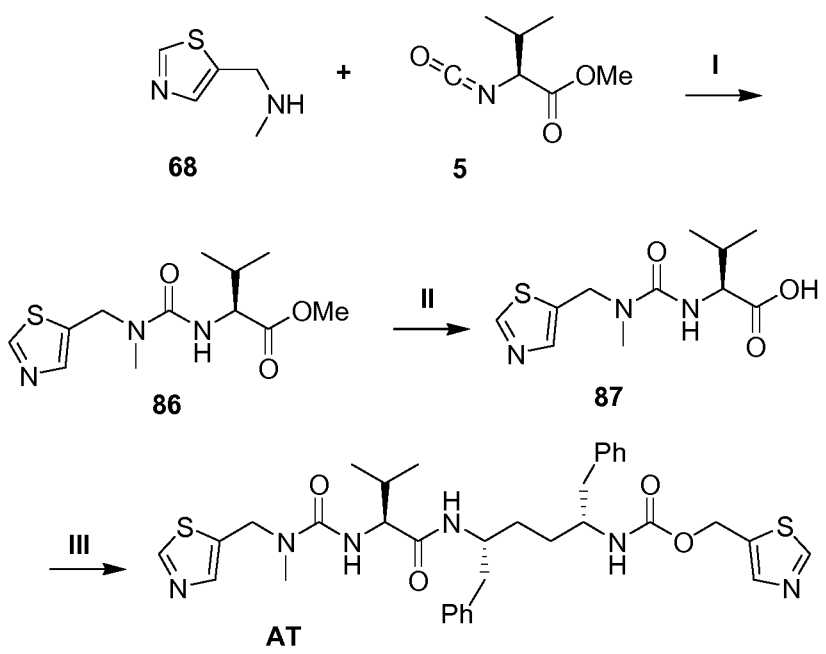
Example AS

[0307] Compound **84** (150 mg, 0.55 mmol) was dissolved in THF (7.15 mL). Compound **8** (225 mg, 0.55 mmol) was added, followed by HOBt (112 mg, 0.83 mmol), iPr_2NEt (393 μL, 2.20 mmol), and EDC (198 μL, 1.11 mmol). The mixture was stirred at 25°C for 12 hours. The solvent was removed under reduced pressure. The residue was diluted ethyl acetate and washed sequentially with saturated aqueous Na_2CO_3, water, and brine. The organic phase was dried over Na_2SO_4, filtered, and evaporated. Purification by flash column chromatography (stationary phase: silica gel; eluent: 7% i-PrOH/CH_2Cl_2) gave Example **AS** (219 mg, 60%). m/z: 663.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.87 (s, 1H); 8.76 (s, 1H); 7.84 (s, 1H); 7.40-7.00 (m, 10H); 6.22 (br s, 1H); 5.73 (br s, 1H); 5.22 (m, 2H); 4.50 (m, 2H); 4.16 (br s, 1H); 4.05 (br s, 1H); 3.75 (m, 1H); 2.93 (s, 3H); 2.90-2.60 (m, 5H); 2.90 (m, 1H); 2.31 (m, 1H); 1.60-1.30 (m, 4H); 1.00-0.80 (m, 6H).

Preparation of Example AT

[0308]

Scheme 37



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O;
III. Cmpd 8, HOBt, EDC, DIPEA, THF

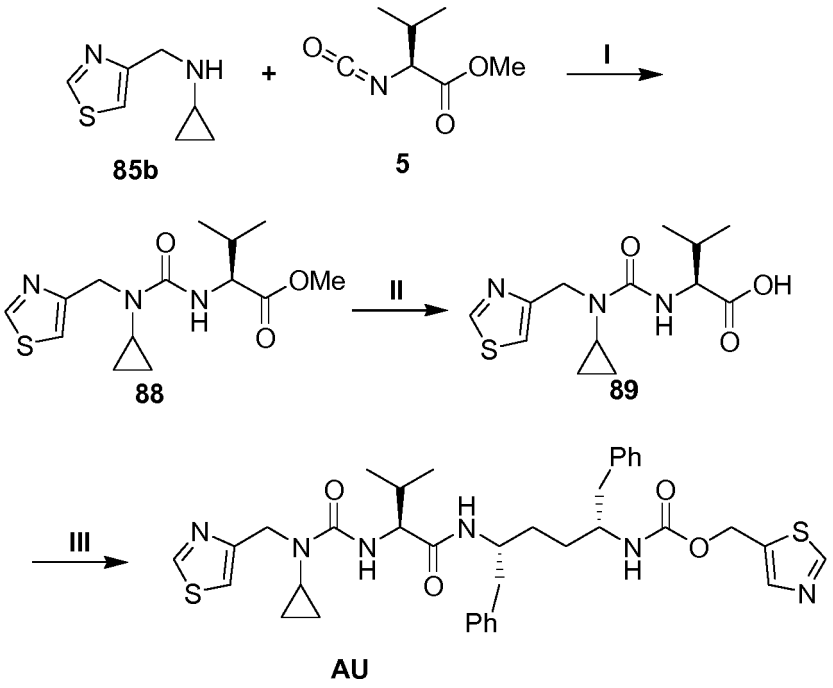
Compound 87

[0309] Compound **87** (386 mg) was prepared from Compound **86** following the same procedure used to prepare Compound 7 from Compound **6,** except that Compound **68** was used was used instead of Compound **4.** m/z 286.0 $(M+H)^+$

Preparation of Example AU

[0310]

Scheme 38



I. DIPEA, CH_2Cl_2; II. LiOH, THF/H_2O; III. Cmpd. 8, HOBt, EDC, DIPEA, THF

Compound 85b

[0311] Compound **85b** was prepared following the same procedure as Compound 4, except that 4-chloromethylthiazole (obtained from TCI America) was used instead of Compound **3.**

Compound 88

[0312] Compound **88** (341 mg) was prepared following the same procedure used to prepare Compound **83,** with the exception that Compound **85b** (300 mg, 1.95 mmol) was used instead of Compound **68.** m/z: 312.0 $(M+H)^+$.

Compound 89

[0313] Compound **89** (341 mg) was prepared following the same procedure for **84,** with the exception that Compound **88** (293 mg, 0.99 mmol) was used instead of Compound **83.** m/z: 298.0 $(M+H)^+$.

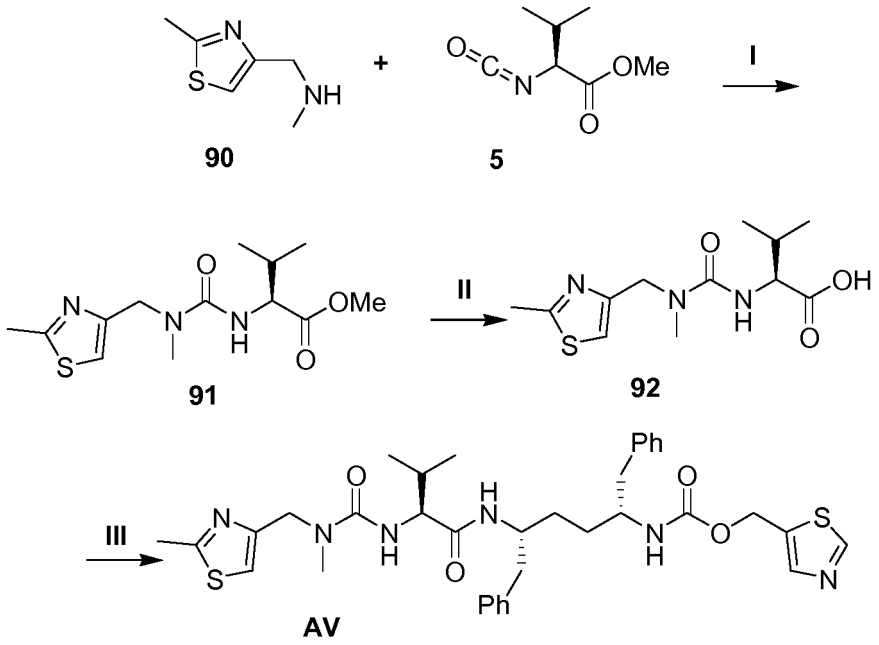
Example AU

[0314] Example **AU** (226 mg, 64%) was prepared following the same procedure used to prepare Example **AS,** with the exception that Compound **89** (150 mg, 0.51 mmol) was used instead of Compound **84.** m/z: 689.1 $(M+H)^+$. ^1H NMR ($CDCl_3$) δ 8.87 (s, 1H); 8.74 (s, 1H); 7.83 (s, 1H); 7.40-7.00 (m, 10H); 6.21 (m, 1H); 5.73 (m, 1H); 5.29 (m, 1H); 5.17 (m, 2H); 4.88 (d, *J*=16 Hz, 1H); 4.47 (d, *J*=16 Hz, 1H); 4.18 (m, 1H); 3.75 (br s, 1H); 2.90-2.60 (m, 6H); 2.51 (br s, 1H); 2.31 (m, 1H); 1.60-1.30 (m, 4H); 1.00-0.80 (m, 10H).

Preparation of Example AV

[0315]

Scheme 39



Compound 90

[0316] Compound **90** (190 mg) was prepared following the procedure used to prepare Compound **4,** except that 4-(chloromethyl)-2-methylthiazole was used instead of Compound **3.** m/z 141.1 (M-H)

Compound 91

[0317] Compound **91** (400 mg) was prepared following the same procedure used to prepare Compound **6** except that Compound **90** was used instead of Compound **4.** m/z 300.0 $(M+H)^+$

Compound 92

[0318] Compound **92** (188 mg) was prepared following the same procedure as Compound 7 except that Compound **91** was used instead of Compound 6. m/z 284.0 $(M-H)^-$

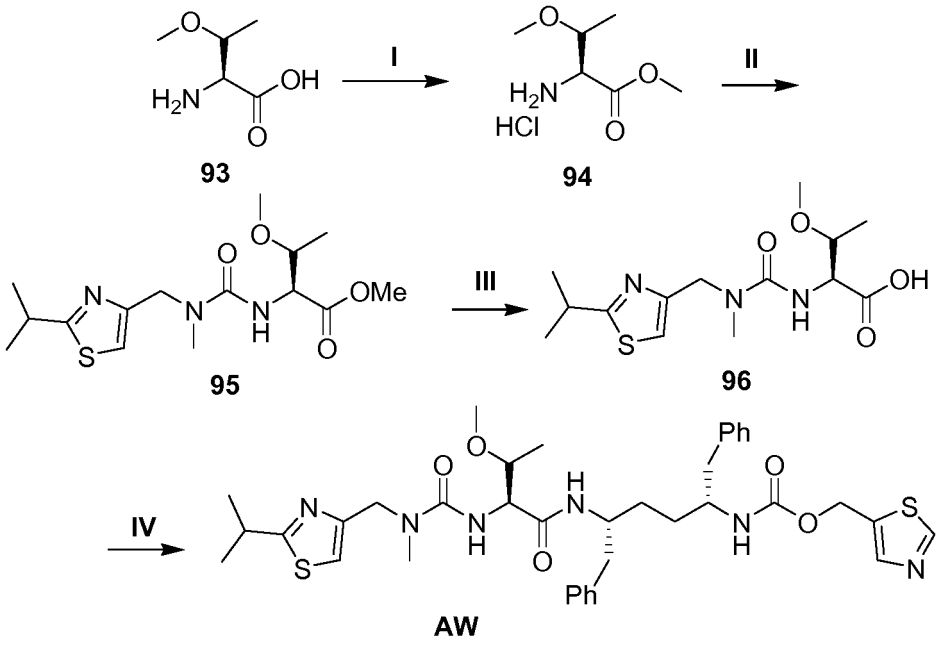
Example AV

[0319] Example **AV** (107 mg) was prepared following the procedure used to prepare Example **C,** except Compound **92** was used instead of Compound **7.** ^1H NMR ($CDCl_3$) δ 8.76 (s, 1H), 7.78 (s, 1H), 7.27-7.07 (m, 10H), 6.93 (s, 1H), 6.25 (m, 2H), 5.39 (m, 1H), 5.19 (m, 2H), 4.37-4.32(m, 2H),4.06 (m, 1H), 3.81 (br s, 1H), 2.83 (m, 4H), 2.65 (br s, 7H), 2.28-2.22 (m, 1H), 1.51-1.37 (m, 4H), 0.82 (m, 6 H): m/z 677.2 $(M+H)^+$

Preparation of Example AW

[0320]

Scheme 40



I.$SOCl_2$/MeOH; II.DIPEA,CH_2Cl_2; III.LiOH,THF/H_2O;
IV. Cmpd 8, HOBt, EDC, IPEA,THF

Compound 93

[0321] Compound 93 is commercially available from TCI, and was used without further purification.

Compound 94

[0322] To a solution of Compound **93** (500 mg, 3.76 mmol) in methanol (20 mL) was added thionyl chloride (0.5 mL, 6.6 mmol) dropwise. The mixture was stirred at 60 ºC for 20 minutes, and concentrated *in vacuo* to gave Compound **94.**

Compound 95

[0323] To a stirred solution of Compound **94** (3.7 mmol) and diisopropylethylamine (1.4 mL, 8.3 mmol) in dichloromethane (50 mL) was added CDI (609 mg, 3.7 mmol). The mixture was stirred for 12 hours. Compound **9** was added, and the mixture was stirred for 12 additional hours. Concentration and purification by flash column chromatography (0-100%: EtOAc/hexane) gave Compound **95** (100 mg). m/z 344.3 $(M+H)^+$

Compound 96

[0324] Compound **96** (39 mg) was prepared following the same procedure used to prepare Compound **7** except that Compound **95** was used instead of Compound **6.** m/z 328.3 $(M-H)^-$

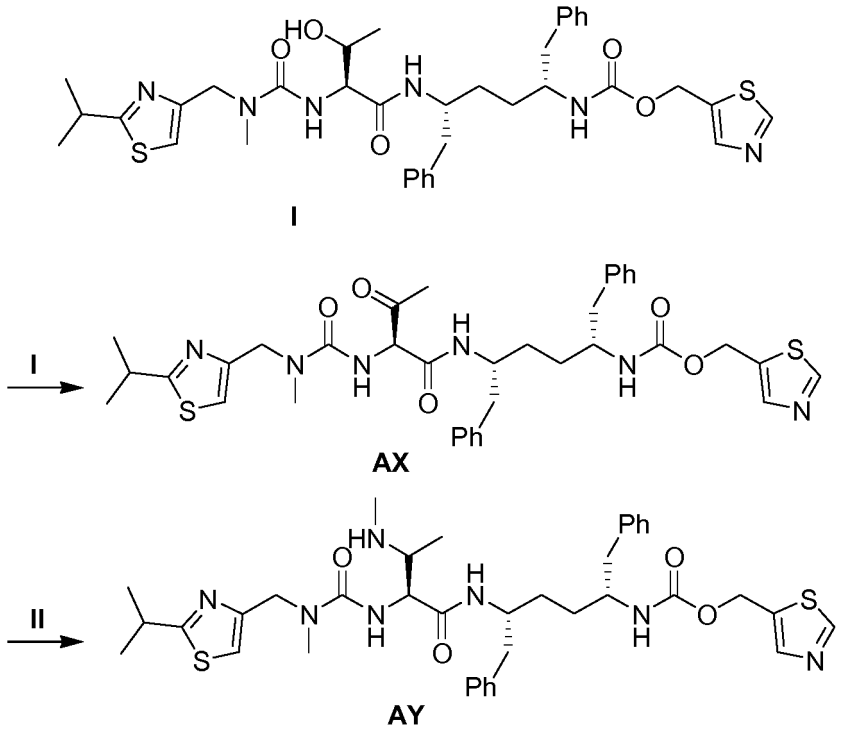
Example AW

[0325] Example **AW** (107 mg) was prepared following the procedure for Example **C,** except that Compound **96** was used instead of Compound 7. ^1H NMR ($CDCl_3$) b 8.79 (s, 1H), 7.82 (s, 1H), 7.27-7.09 (m, 10H), 6.95 (s, 1H), 6.23 (m, 1H), 6.14 (s, 1H), 5.22 (s, 3H), 4.45 (m, 2 H), 4.35-4.0 (m, 3 H), 3.8 (m, 1 H), 3.6 (m, 1 H), 3.25 (s, 3H), 3.21 (m, 2H), 2.95 (s, 3 H), 2.8-2.6 (m, 4 H), 2.0-1.4 (m, 4 H), 1.25 (m, 4 H), 1.05 (m,4H): m/z 721.3 $(M+H)^+$

Preparation of Examples AX and AY

[0326]

Scheme 41



Example AX

[0327] To a solution of Example I (650 mg, 1.00 mmol) in DMSO (3.5 mL) was added triethylamine (0.5 mL). The mixture was stirred for 30 minutes. Pyridine SO_3 was added to the mixture at 5oC then stirred for 60 minutes. The mixture was poured on to ice-water, then stirred for 30 minutes. The mixture was diluted with EtOAc and washed with water, sat. $NaHCO_3$, and brine. Concentration gave Example **AX**. m/z 705.2 $(M+H)^+$

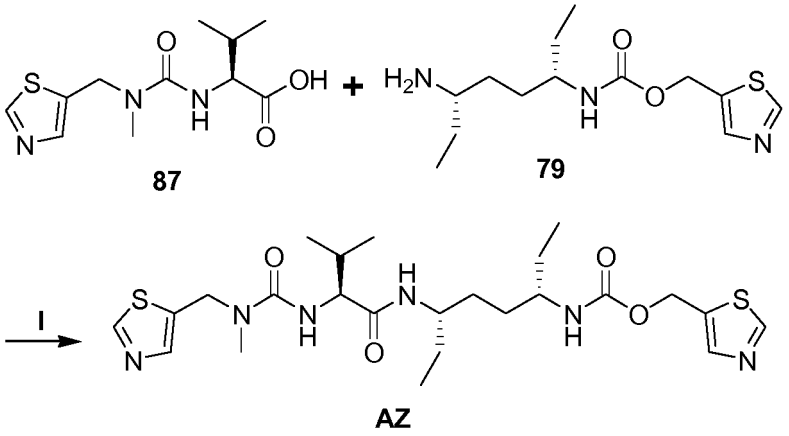
Example AY

[0328] To a stirred solution of Example **AX** (70 mg, 0.099 mmol) and methylamine (1.5 mL, 2M) in MeOH (1.5 mL) was added AcOH (119 mg, 1.99 mmol). The mixture was stirred for 2 hours. $NaBH(OAc)_3$ (94 mg) was added, and the mixture was stirred for 2 hours. Concentration and purification by prep. HPLC gave Example **AY** (30 mg). ^1H NMR ($CDCl_3$) b 8.79 (s, 1H), 7.82 (s, 1H), 7.27-7.09 (m, 10H), 6.95 (s, 1H), 6.23 (m, 1H), 6.14 (s, 1H), 5.22 (s, 2 H), 4.45 (m, 1 H), 4.35-4.0 (m, 4 H), 3.8 (m, 1 H), 3.6 (m, 1 H), 3.21 (m, 1 H), 2.95 (s, 3 H), 2.93 (s, 3H), 2.8-2.6 (m, 4 H), 2.0-1.4 (m, 4 H), 1.25 (m, 4 H), 1.05 (m, 4H): m/z 720.3 $(M+H)^+$

Preparation of Example AZ

[0329]

Scheme 42



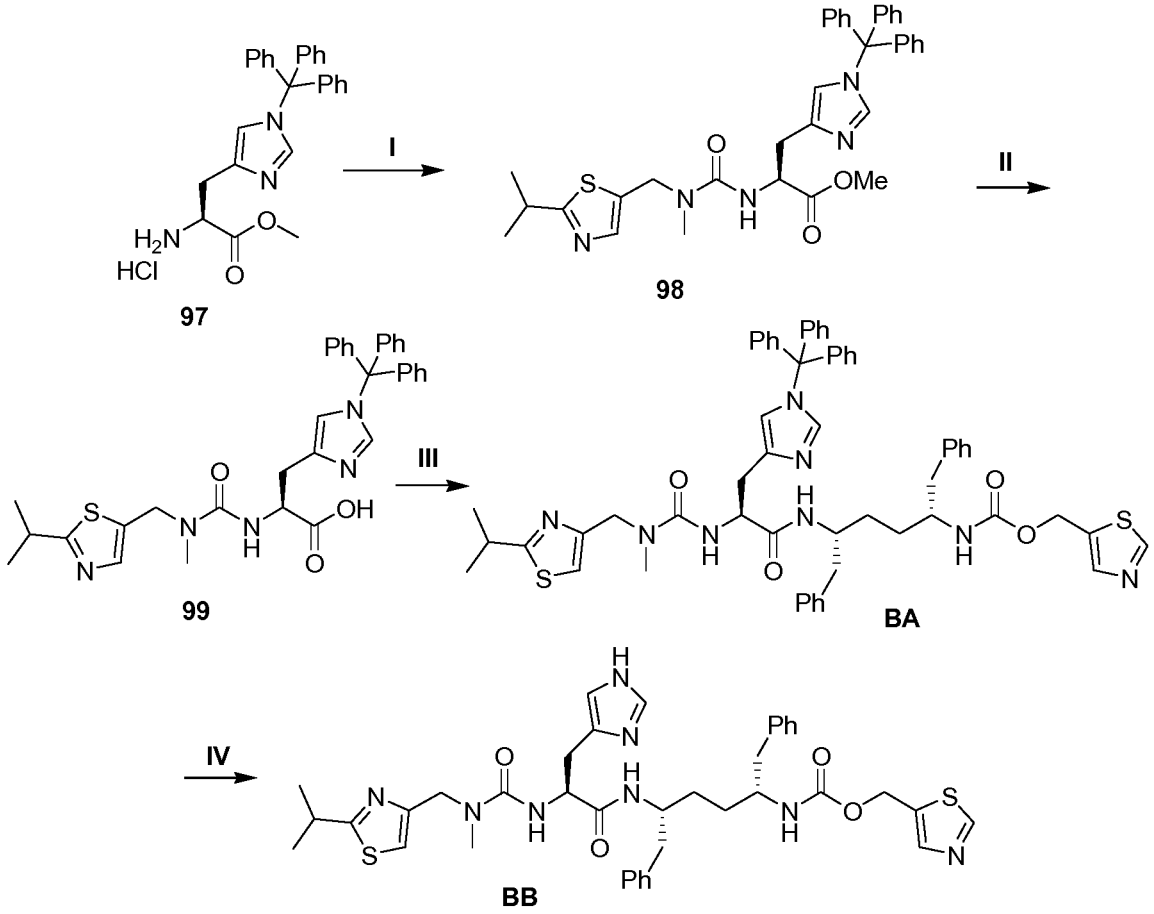
Example AZ

[0330] Compound **AZ** (61 mg) was prepared following the procedure for Example **C,** except that Compound **87** was used instead of Compound **7** and Compound **79** was used instead of Compound **8.** ^{1}H NMR ($CDCl_3$) b 8.77 (s, 1H), 8.72 (s, 1H), 7.78 (s, 1H), 7.71 (s, 1H), 6.23 (d, 1H), 5.28-5.24 (m, 2H), 4.85 (d, 1H), 4.71-4.57 (m, 2H), 4.08-4.03 (m, 1H), 3.78 (br s, 1H), 3.51 (br s, 1H), 2.87 (s, 3H), 2.33 (br s, 1H), 2.13-2.06 (m, 1H), 1.49-1.33 (m, 8H), 0.93-0.80 (m, 12 H): m/z 539.2 $(M+H)^+$

Preparation of Examples BA and BB

[0331]

Scheme 43



I. a. CDI/iPr_2NEt; b. Compound 9; II.a. NaOH/THF/H_2O; b. HCl;
III. Cmpd 8/EDC/HOBt, IPEA, THF: IV. Et_3SiH, TFA

Compound 97

[0332] Compound 97 is commercially available from TCI, and was used as received.

Compound 98

[0333] To a stirred solution of Compound **97** (1 g, 2.2 mmol) and diisopropylethylamine (1.6 mL, 8.9 mmol) in dichloromethane (26 mL) was added CDI (362 mg, 2.2 mmol). The mixture was stirred for 12 hours. Compound **9** was added, and the mixture was stirred for 12 additional hours. Concentration and purification by flash column chromatography (0-8%: MeOH/DCM) gave Compound **98** (1.2 g). m/z 608.1 $(M+H)^+$

Compound 99

[0334] Compound **99** (1.2 g) was prepared following the same procedure used to prepare Compound **67,** with the exception that Compound **98** was used instead of Compound **66.** m/z 592.2 $(M-H)^-$

Example BA

[0335] Example **BA** (111 mg) was prepared following the procedure used to prepare Example **C,** except that Compound **99** was used instead of Compound **7.** m/z 986.1 $(M+H)^+$

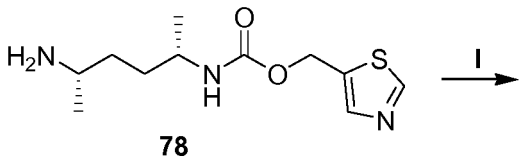
Example BB

[0336] To a stirred solution of Example **BA** (111 mg, 0.113 mmol) and TFA (1.4 mL) was added Et_3SiH (0.1 mL). The mixture was stirred for 60 minutes, then concentrated and partitioned with EtOAc and sat. $NaHCO_3$, followed by extraction with EtOAc (2X) and drying over Na_2SO_4. Concentration and purification by flash column chromatography (0-15%: MeOH/DCM) gave Example **BB** (50 mg).
^{1}H-NMR ($CDCl_3$) $\delta_{(ppm)}$8.75 (s, 1 H), 7.79 (s, 1 H), 7.42 (s, 1 H), 7.22-7.12 (m, 9H), 6.99-6.96 (m, 2H), 6.86 (s, 1H), 6.71 (m, 2H), 5.51 (br s, 1 H), 5.17 (m, 2H), 4.57-4.52 (m, 1 H), 4.39-4.35 (m, 2 H), 4.07 (m, 1 H), 3.74 (br s 1 H), 3.28-3.19 (m, 1H,), 3.09-2.76 (m, 6 H), 3.65-2.58 (m, 3 H), 1.49 (m, 2 H), 1.36-1.20 (m, 8 H); m/z 743.2 $(M+H)^+$

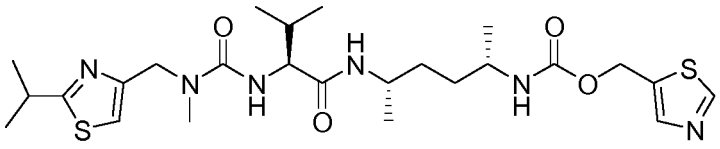
Preparation of Example BC

[0337]

Scheme 44



78



BC

I. HOBt, EDC, DIPEA, THF, Cmpd 29

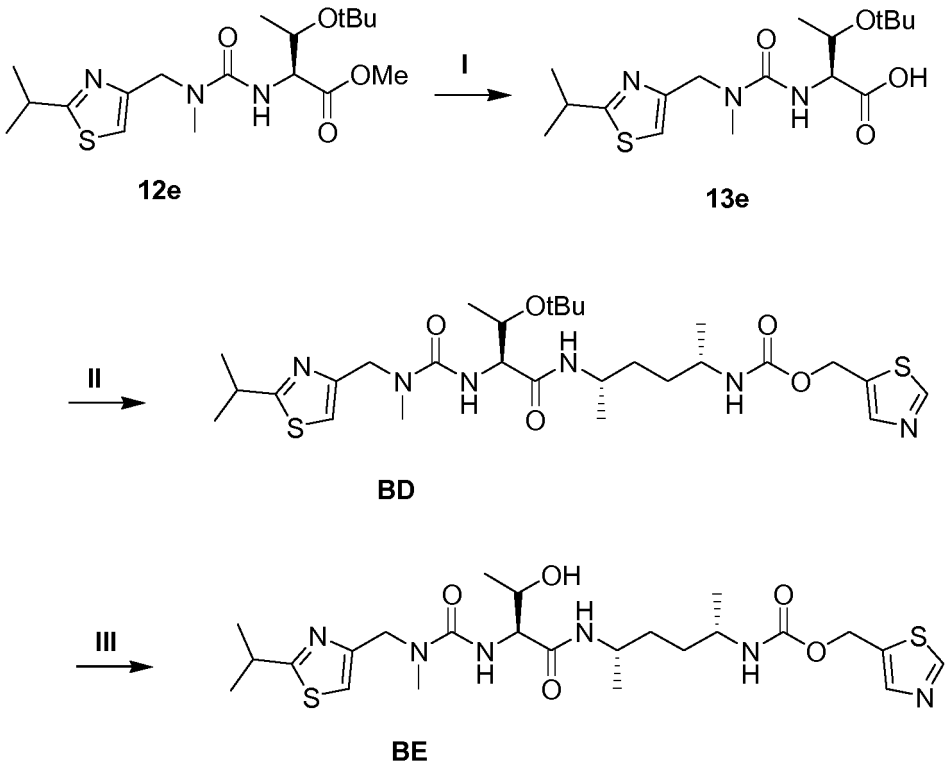
Example BC

[0338] Example **BC** (95 mg) was prepared following the procedure used to prepare Example C, except that Compound **29** was used instead of Compound **7,** and Compound **78** was used instead of Compound 8. ^{1}H NMR ($CDCl_3$) b 8.75 (s, 1H), 7.80 (s, 1H), 6.93 (s, 1H), 6.28 (d, 1H), 6.18 (m, 1H), 5.26-5.21 (m, 3H), 4.47-4.30 (m, 2H), 4.11-4.00 (m, 1H), 3.91 (br s, 1H), 3.59 (br s, 1H), 3.28 (m, 1H), 2.97-2.90 (m, 3H), 2.26-2.19 (m, 1H), 1.39-1.24 (m, 10H), 1.09-1.01 (m, 6 H), 0.94-0.86 (m, 6 H): m/z 553.1 $(M+H)^+$

Preparation of Examples BD and BE

[0339]

Scheme 45



I. LiOH, THF/H_2O; II. Cmpd. 78, HOBt, EDC, DIPEA, THF; III. a. neat TFA; b. NaOH, THF, H_2O

Example BD

[0340] Example **BD** (148 mg) was prepared following the procedure used to prepare Example **C,** except that Compound **13e** was used instead of Compound **7,** and Compound **78** was used instead of amine **8.** m/z 611.1 $(M+H)^+$

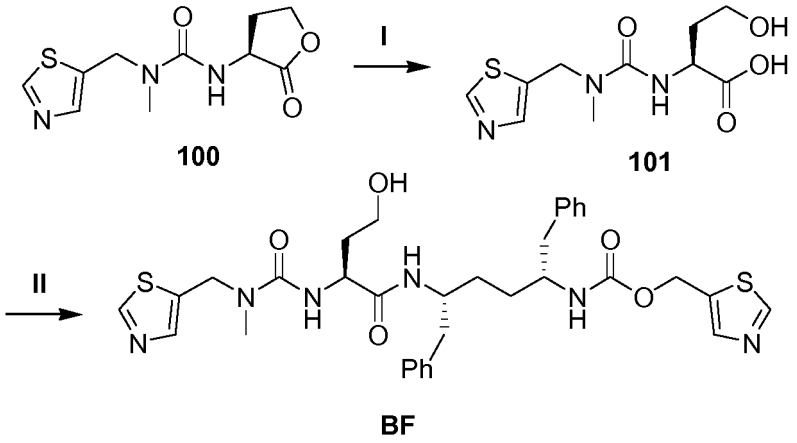
Example BE

[0341] Example **BD** (148 mg, 0.242 mmol) was dissolved in TFA (3 mL) and allowed to stir at 25 °C for 3 hours. The solvent was removed under reduced pressure and the residue was diluted with THF (3 mL) and 2N aqueous NaOH was added until pH 10. The mixture was allowed to stir for 20 min and extracted with EtOAc. The organic layer was washed sequentially with water and brine, dried over Na_2SO_4, filtered, and evaporated. Purification by flash chromatography (0-10% MeOH/CH_2Cl_2) gave Example **BE** (109 mg). ^1H NMR ($CDCl_3$) b 8.75 (s, 1H), 7.80 (s, 1H), 6.97-6.94 (d, 1 H), 6.90 (s, 1H), 6.32 (br s, 1 H), 5.26-5.22 (m, 2H), 5.12 (d, 1H), 4.51-4.39 (m, 3H), 4.25-4.22 (m, 2 H), 3.87 (br s, 1H), 3.62 (br s, 1 H), 3.27-3.18 (m, 1 H), 2.94 (s, 3 H), 1.41-1.31 (m, 10 H), 1.13-1.00 (m, 9 H). m/z: 555.1 $(M+H)^+$.

Preparation of Example BF

[0342]

Scheme 46



Compound 100

[0343] Compound **100** was prepared using the same method used to prepare Compound **122,** except that Compound **9** was replaced with Compound **68** (*see* Scheme 70).

Compound 101

[0344] Compound **100** (108 mg, 0.423 mmol) was dissolved in THF (2 mL), then 847 μl of 1 M $LiOH/H_2O$ was added. After stirring overnight, 843 μl of 1 N HCl was added. Concentration gave Compound **101.**

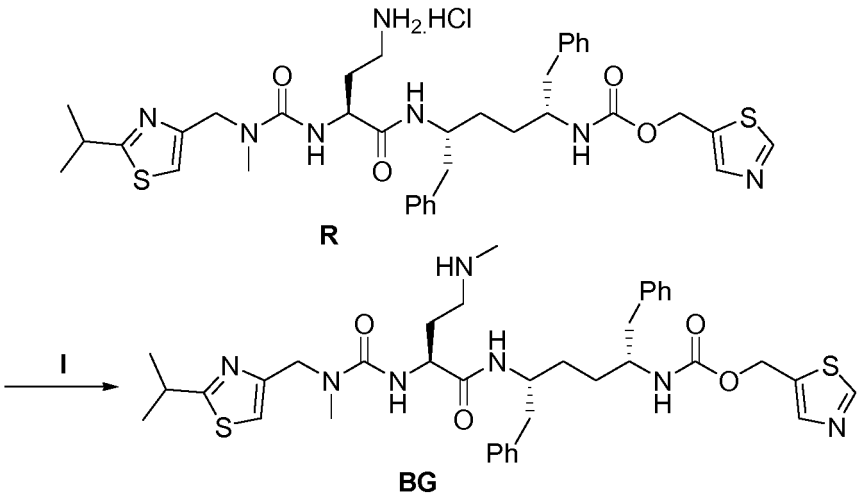
Example BF

[0345] Example **BF** (24 mg) was prepared following the procedure used to prepare Example **C,** except that Compound **101** was used instead of Compound 7. ^1H NMR ($CDCl_3$) δ 8.77 (s, 1H), 8.73 (s, 1H), 7.80 (s, 1H), 7.74 (s, 1H), 7.27-7.10 (m, 10H), 6.55-6.52 (d, 1H), 5.84 (d, 1 H), 5.21-5.19 (m, 3 H), 4.77-4.53 (m, 2H), 4.39 (br s, 1 H), 4.11-3.99 (m, 2 H), 3.81 (br s, 1H), 3.58 (m, 2 H), 2.86 (s, 3 H), 2.81-1.72 (m, 5H), 2.04 (m, 1 H), 1.85 (m, 1 H), 1.66-1.37 (m, 6 H): m/z 665.2 $(M+H)^+$

Preparation of Example BG

[0346]

Scheme 47



I. Ethyltrifluoroacetate, MeI, Cs_2CO_3, THF

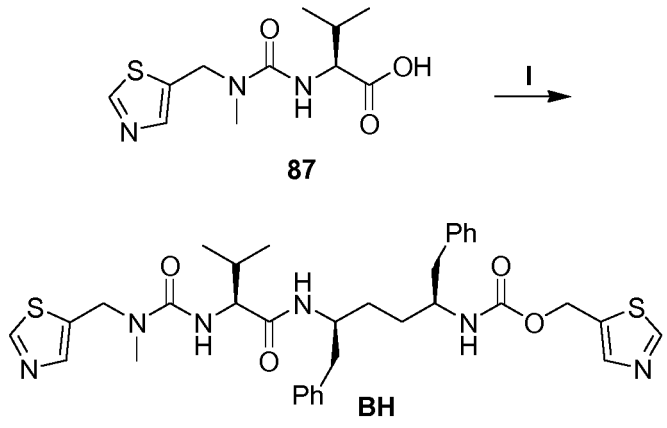
Example BG

[0347] Example **R** (102 mg, 0.137 mmol) was dissolved in THF (2 mL), then 2 mL of ethyltrifluoroactate was added. Then 1.3 eq of MeI and excess Cs_2CO_3 were added. After stirring for 1 day, the mixture was partitioned with EtOAc and sat. Na_2CO_3, extracted with EtOAc (2X), and dried over Na_2SO_4. Purification by flash chromatography (0-20% MeOH/CH_2Cl_2) gave Example **BG** (6.5 mg). ^{1}H NMR (CD_3OD) b 9.94 (s, 1H), 8.27 (s, 1H), 7.73 (s, 1H), 7.30-7.10 (m, 10H), 5.29, 5.17 (d 2H), 4.72 (s, 3H), 4.29 (m, 1H), 4.15 (br s, 1H), 3.83 (br s, 1H), 3.61 (m, 2H), 3.07 (s, 3H), 2.93 (m, 2H), 2.82-2.70 (m, 4H), 2.68-2.58 (m, 2H), 2.42 (s, 3H), 2.05 (m, 2H), 1.70-1.40 (m, 10H). m/z: 720.2 $(M+H)^+$.

Preparation of Example BH

[0348]

Scheme 48



I. amine 59, HOBt, EDC, DIPEA, THF

Example BH

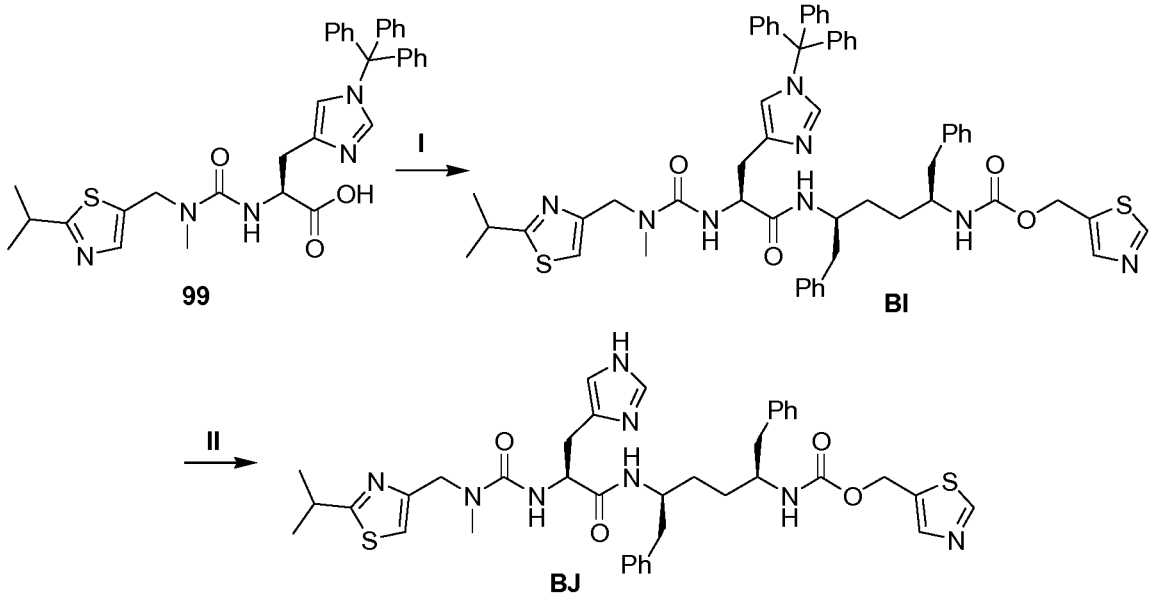
[0349] Example **BH** (78 mg) was prepared following the procedure used to prepare Example **C,** except that Compound **87** was used instead of Compound 7, and Compound 46 was used instead of Compound **8.** ^{1}H NMR ($CDCl_3$) b 8.73 (s,

1H), 8.68 (s, 1H), 7.76 (s, 1H), 7.68 (s, 1H), 7.18-7.09 (m, 10H), 6.26 (m, 1H), 5.76 (m, 1H), 5.22-5.18 (m, 4H), 4.71-4.65 (d, 1H), 4.46-4.40 (d, 1H), 4.11-4.04 (m, 2H), 3.81 (br s, 1H), 3.14 (br s, 1H), 2.83 (s, 3H), 2.76-2.52 (m, 4H), 1.88 (m, 1H), 1.51-1.37 (m, 2H), 0.73-0.69 (m, 6 H) m/z 663.2 $(M+H)^+$

Preparation of Examples BI and BJ

[0350]

Scheme 49



I. Cmpd. 46/EDC/HOBt, IPEA, THF: II. Et_3SiH, TFA

Example BI

[0351] Example **BI** (1.78 g) was prepared following the procedure used to prepare Example C, except that Compound **99** was used instead of Compound **7,** and Compound **46** was used instead of Compound **8.** m/z 986.1 $(M+H)^+$

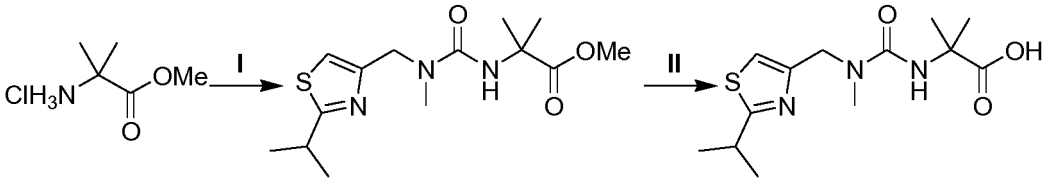
Example BJ

[0352] Example **BJ** (728 mg) was prepared following the procedure used to prepare Example **BB,** except that Example **BI** was used instead of Example **BA.** ^{1}H-NMR (CDCl3) ◎◎ 8.75 (s, 1 H), 7.79 (s, 1 H), 7.42 (s, 1 H), 7.22-7.12 (m, 9H), 6.99-6.96 (m, 2H), 6.86 (s, 1H), 6.71 (m, 2H), 5.51 (br s, 1 H), 5.17 (m, 2H), 4.57-4.52 (m, 1 H), 4.39-4.35 (m, 2 H), 4.07 (m, 1 H), 3.74 (br s 1 H), 3.28-3.19 (m, 1H,), 3.09-2.76 (m, 6 H), 3.65-2.58 (m, 3 H), 1.49 (m, 2 H), 1.36-1.20 (m, 8 H); m/z 743.2 $(M+H)^+$

Preparation of Compounds 104-115

[0353]

Scheme 50



102 **103** **104**

I. a. CDI, DIPEA, MeCN; b. Cmpd. 9, MeCN. II. 1M LiOH, THF.

Compound 102

[0354] Compound **102** is commercially available from Aldrich Chemical Co., and was used without further purification.

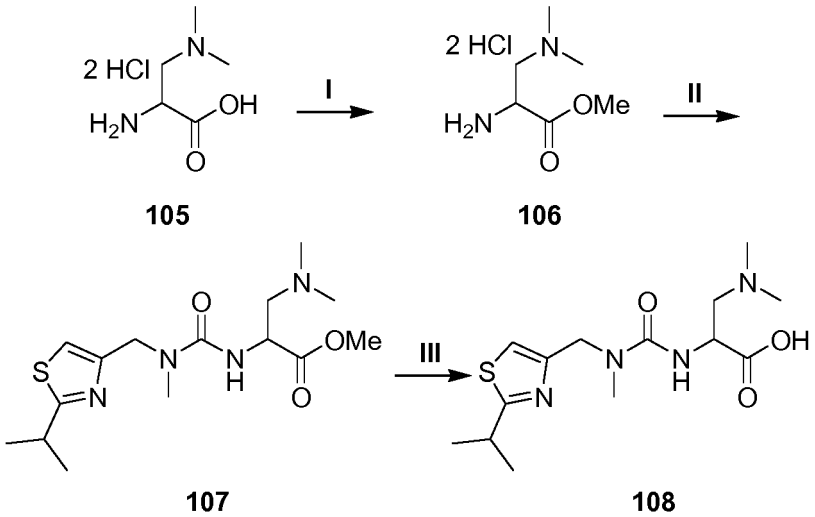
Compound 103

[0355] Compound **102** (5.5 mmol) was suspended in MeCN (55 mL) and DIPEA (8.25 mmol) was added. Carbonyl diimidazole (5.5 mmol) was diluted in MeCN (20 mL) and the solution added slowly to the reaction mixture over 45 min. The resulting mixture was allowed to age overnight. Compound 9 (5.5 mmol) was diluted in MeCN (10 mL) and treated with DIPEA (8.25 mmol) before being added to the reaction mixture, which was then allowed to age overnight. The volatiles were removed *in vacuo* and the residue taken up in EtOAc (50 mL) and washed with 1M HCl (50 mL). The layers were separated and the aqueous layer extracted with EtOAc (3 X 50 mL). The combined organic layers were washed with sat. Na_2CO_3 until the pH of the washes was ~ pH 8. A brine wash (30 mL) was followed by drying over anhydrous $MgSO_4$. Following concentration *in vacuo*, the residue was purified on SiO_2 (0-65% EtOAc/hex) to provide 0.340 g (20%) of Compound **103** as an amorphous white solid (*m/z* 314.0 $(M+H)^+$).

Compound 104

[0356] Compound **103** (1.1 mmol) was diluted in THF (5 mL) and treated with freshly prepared 1M LiOH (2.2 mmol). The biphasic reaction was stirred vigorously for 2 h before being quenched with 1M HCl (3 mmol). The reaction was extracted with EtOAc (5 X 15 mL) and the combined organics were washed with brine (30 mL), dried over anhydrous Na_2SO_4 and concentrated to provide 0.282 g (86%) of Compound **104** as an amorphous white powder that was used with further purification ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.06 (s, 1H); 4.37 (s, 1H); 3.28 (p, *J* = 6.9 Hz, 1H); 3.00 (s, 3H); 1.62 (s, 6H); 1.39 (d, *J* = 6.9 Hz, 6H).

Scheme 51



105 **106** **107** **108**

I. HCl, MeOH; II. a. CDI, DIPEA, MeCN; b. Cmpd. 9, MeCN. III. 1M LiOH, THF.

Compound 105

[0357] Compound **105** is commercially available from Aldrich Chemical Co., and was used without further purification.

Compound 106

[0358] Racemic Compound **105** (12.2 mmol) was diluted in MeOH (100 mL). HCl/dioxane solution (4M, 25 mmol) was added and the solution was refluxed overnight. Volatiles were removed *in vacuo* to produce 2.60 g (97%) of Compound **106** as a racemic mixture. The foamy white solid was used without further purification (*m*/*z* 147.0 $(M+H)^+$).

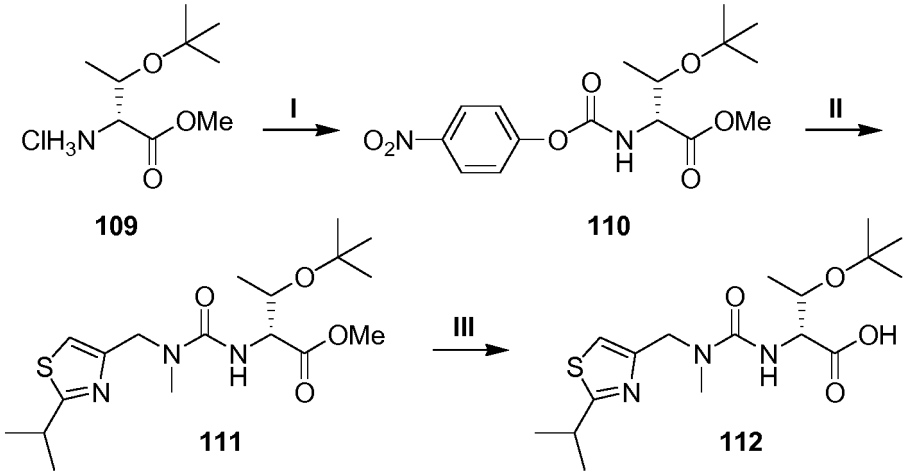
Compound 107

[0359] Compound **106** (5 mmol) was diluted in MeCN (65 mL) and treated with DIPEA (25 mmol). The resulting solution was added slowly via addition funnel to a solution of CDI (5 mmol) in MeCN (30 mL) and allowed to age overnight. Compound **9** (5 mmol) and DIPEA (3 mmol) were added to the reaction solution which was allowed to age overnight. The volatiles were removed *in vacuo* and the residue was taken up in EtOAc and sat. Na_2CO_3 (30 mL each). The aqueous layer was extracted with EtOAc (3 X 25 mL) and the combined organics were washed with brine (50 mL) and dried over anhydrous $MgSO_4$. Following concentration *in vacuo*, purification by column chromatography on SiO_2 (0-10% MeOH/DCM) provided 0.36 g (21%) of racemic Compound **107** as a yellow oil (*m*/*z* 343.1 $(M+H)^+$).

Compound 108

[0360] Compound **107** (1.05 mmol) was taken up in THF (5 mL) and treated with freshly prepared 1M LiOH solution (2.1 mmol). The solution was stirred vigorously for 2 h and quenched with 1M HCl (2.1 mmol). The volatiles were removed *in vacuo*, and the resulting oil was azeotroped with toluene until a quantitative yield of racemic Compound **107** was produced as an amorphous white solid that was used without further purification (*m*/*z* 329.1 $(M+H)^+$).

Scheme 52



I. *p*-$O_2NC_6H_4O(CO)Cl$, NMM, DCM, 0 °C to rt; II. Cmpd. 9, Et_3N, DMAP, THF, 70 °C; III. 1M LiOH, THF

Compound 109

[0361] Compound **109** is commercially available from Bachem, and was used as received.

Compound 110

[0362] Compound **109** (4.1 mmol) was diluted in DCM (5 mL) and treated with N-methylmorpholine (8.2 mmol). This solution was added slowly to a DCM (5 mL) solution of 4-nitrophenyl chloroformate (4.1 mmol) at 0 °C. The reaction was then allowed to warm to room temperature overnight. The volatiles were removed *in vacuo* and the residue was taken up in EtOAc and sat. Na_2CO_3. The aqueous layer was extracted with EtOAc (3 X 10 mL) and the combined

organics were washed with brine (30 mL) prior to being dried over anhydrous Na_2SO_4. Following concentration *in vacuo*, the residue was purified by column chromatography on SiO_2 (0-25% EtOAc/Hex) to produce 0.75 g (51%) of Compound **110** as an amorphous white solid (*m/z* 354.8 $(M+H)^+$).

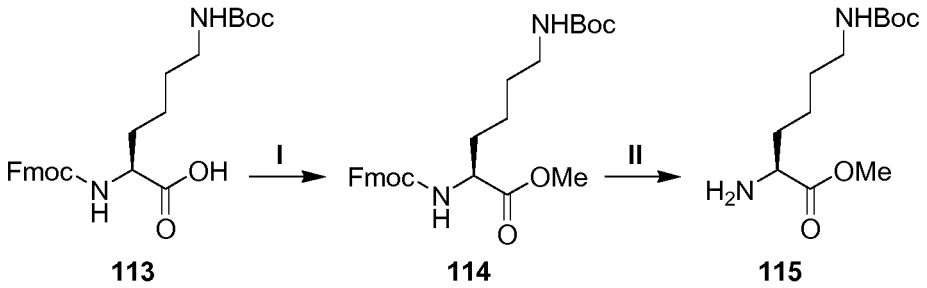
Compound 111

[0363] Compound **110** (1.1 mmol) was diluted in THF (3.5 mL). Compound **9** (1.4 mmol) was diluted in THF (3 mL), treated with Et_3N (2.8 mmol) and transferred to the reaction solution. DMAP (0.11 mmol) was added and the reaction was heated to 70 °C for 2 h. After cooling to room temperature, EtOAc (10 mL) and sat. Na_2CO_3 were added. The aqueous phase was extracted with EtOAc (3 X 10 mL) and the combined organics were washed with sat. Na_2CO_3, H_2O, and brine (15 mL each). After drying over anhydrous $MgSO_4$, volatiles were removed *in vacuo* and the residue was purified by column chromatography on SiO_2 (0-50% EA/hex) to produce 0.346 g (82%) of Compound **111** (*m/z* 386.0 $(M+H)^+$).

Compound 112

[0364] Compound **111** (0.88 mmol) was taken up in THF (4 mL) and treated with freshly prepared 1M LiOH (1.8 mmol). The reaction mixture was stirred vigorously for 1.5 h and quenched with 1M HCl (2.5 mmol). The reaction mixture was extracted with EtOAc (3 X 10 mL),and the combined organics were washed with brine (30 mL) and dried over anhydrous Na_2SO_4. Concentration *in vacuo* produced 0.300 g (92%) of Compound **112** as a colorless film that was used without further purification (*m/z* 372.0 $(M+H)^+$).

Scheme 53



113 **114** **115**

I. $TMSCHN_2$, THF/MeOH; II. piperidine, DMF

Compound 113

[0365] Compound **113** is commercially available from Chem-Impex, and was used without further purification.

Compound 114

[0366] Compound **113** (3.2 mmol) was diluted in THF (15 mL). $TMSCHN_2$ (3.2 mmol) was added slowly, followed by MeOH (5 mL). The solution rapidly became colorless, and heavy evolution of gas was observed. After aging overnight, the volatiles were removed *in vacuo* and the residue purified by column chromatography on SiO_2 (0-50% EtOAc/hex) to produce 0.805 g (52%) of Compound **114** (*m/z* 505.2 $(M+Na)^+$).

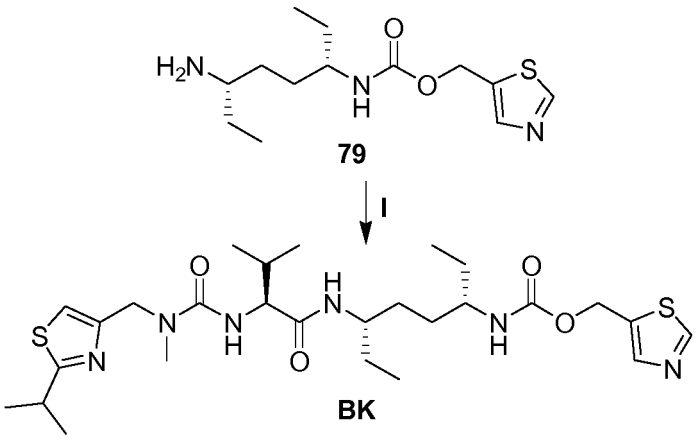
Compound 115

[0367] Compound **114** (1.7 mmol) was diluted in DMF (4 mL) and piperidine (1 mL) was added. After 30 min, the volatiles were removed *in vacuo* and the residue was purified by column chromatography on SiO_2 (0-5% MeOH/DCM) to provide 0.414 (94%) of Compound **115** as an amorphous white solid (*m/z* 261.0 $(M+H)^+$).

Preparation of Example BK

[0368]

Scheme 54



I. Cmpd. 29/EDC/HOBt/DIPEA/THF.

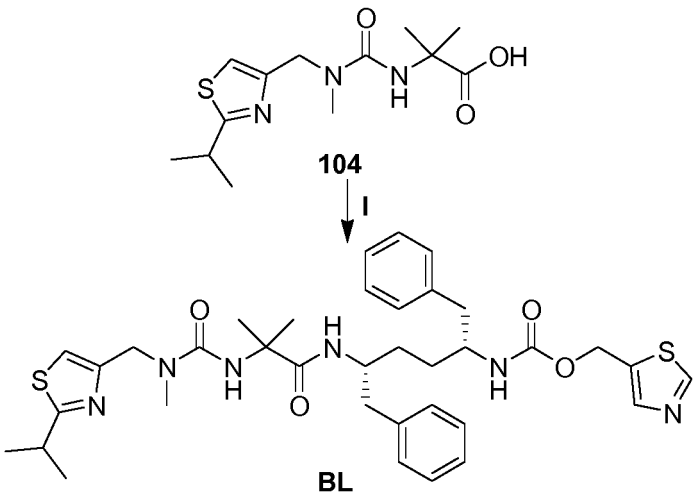
Compound BK

[0369] Compound **79** (0.70 mmol) and Compound **29** (0.91 mmol) were combined in THF (7 mL). HOBt (0.91 mmol), DIPEA (1.05 mmol) and EDC (0.91 mmol) were added consecutively at room temperature and the reaction was allowed to age overnight. The volatiles were removed *in vacuo* and the residue taken up in 3/1 $CHCl_3$/IPA and sat. Na_2CO_3 (15 mL each). The aqueous layer was extracted with 3/1 $CHCl_3$/IPA (3 X 10 mL) and the combined organics were washed with sat. Na_2CO_3, water, and brine (15 mL each). Following drying over anhydrous $MgSO_4$, the volatiles were removed *in vacuo* and the residue was purified by column chromatography on SiO_2 (0-10% MeOH/DCM) to produce 8.5 mg (2%) of Compound **BK** *m/z* 581.2 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.91 (s, 1H); 7.89 (s, 1H); 7.15 (s, 1H); 6.52-6.0 (br m, 2H); 5.26 (s, 2H); 5.18 (br d, *J* = 8.1 Hz, 1H); 4.55 (s, 2H); 4.06 (br s, 1H); 3.79 (br s, 1H); 3.48 (m, 2H); 3.09 (s, 3H, minor rotamer); 3.01 (s, 3H, major rotamer); 2.34 (m, 1H); 1.60-1.30 (m, 8H); 1.42 (d, *J* = 6.9 Hz, 6H); 0.98 (t, *J* = 7.2 Hz, 6H); 0.86 (m, 6H).

Preparation of Example BL

[0370]

Scheme 55



I. Cmpd. 8/EDC/HOBt/DIPEA/THF.

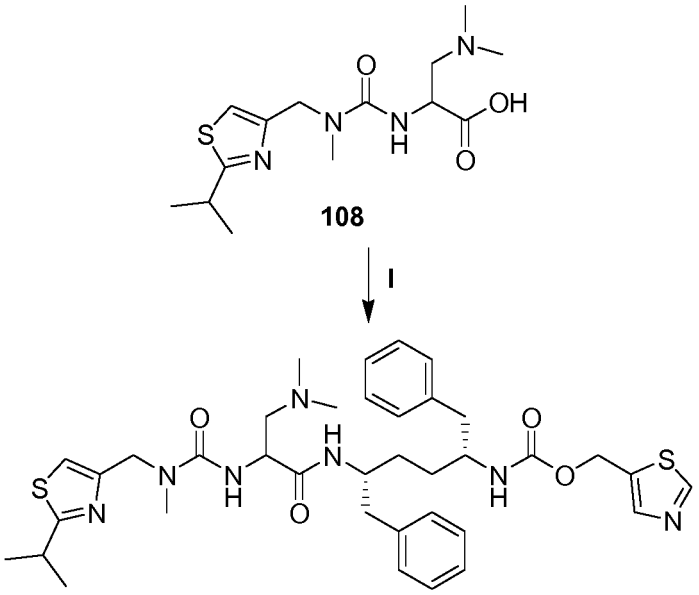
Example BL

[0371] Example **BL** was prepared in a similar fashion to Example **BK** using Compound **104** (0.26 mmol) and Compound **8** (0.29 mmol) to produce 0.087 g (64%) of Example **BL** as an amorphous white solid *m/z* 691.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.82 (s, 1H); 7.82 (s, 1H); 7.30-7.10 (m, 11H); 7.06 (s, 1H); 6.54 (d, *J* = 9.6 Hz, 1H); 5.89 (d, *J* = 8.4 Hz, 1H); 5.22 (s, 1H); 5.07 (m, 1H); 4.45 (AB d, *J* = 16.5 Hz, 1H); 4.37 (AB d, *J* =15.6 Hz, 1H); 4.07 (m, 1 H); 3.68 (m, 1H); 3.40 (m, 1H); 3.06 (s, 3H, minor rotamer); 2.89 (s, 3H, major rotamer); 2.90-2.54 (m, 4H); 1.60-1.25 (m, 16H).

Preparation of Example BMa and BMb

[0372]

Scheme 56



I. Cmpd. 8/EDC/HOBt/DIPEA/THF.

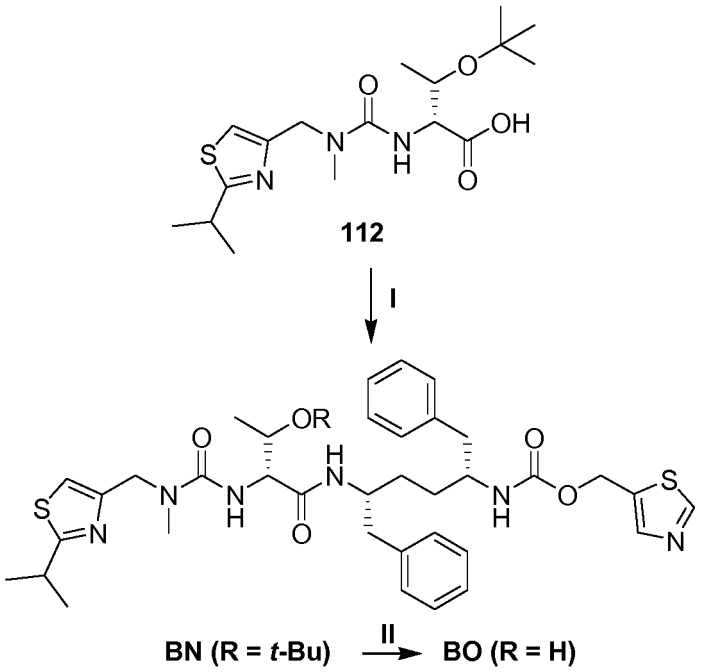
Examples BMa and BMb

[0373] Examples **BMa** and **BMb** were prepared in a similar fashion to Compound **BK** using racemic Compound **108** (0.36 mmol) and Compound **8** (0.28 mmol). The enantiomeric products were separated by preparatory HPLC (Chiralcel OD-H (250 X 4.6 mm, 70:30 Heptane/IPA, 30 min) to produce 0.008 g (4%) of enantiomer **BMa** (HPLC R_T = 11.71 min) *m/z* 720.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.73 (s, 1H); 7.78 (s, 1H); 7.41 (br s, 1H); 7.30-7.00 (m, 11H); 6.94 (s, 1H); 5.40 (br s, 1H); 5.18 (br s, 2H); 4.56 (AB d, *J* = 15 Hz, 1H); 4.48 (AB d, *J* = 16 Hz, 1H); 4.39 (br s, 1H); 4.05 (br s, 1H); 3.73 (br s, 1H); 3.25 (s, 3H, minor rotamer); 3.23 (m, 1H); 2.98 (s, 3H, major rotamer); 2.82-2.30 (m, 10H); 1.60-1.20 (m, 6H); 1.32 (d, *J* = 7 Hz, 6H) and 0.010 g (5%) of enantiomer **BMb** (HPLC R_T = 15.41 min). (*m/z* 720.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.78 (s, 1H); 7.83 (s, 1H); 7.38 (br d, *J* = 8 Hz, 1H); 7.30-7.7.05 (m, 11H); 7.02 (s, 1H); 5.52 (d, *J* = 9 Hz, 1H); 5.25 (AB d, *J* = 13 Hz, 1H); 5.21 (AB d, *J* = 13 Hz, 1H); 4.85-4.62 (m, 2H); 4.44 (d, *J* = 16 Hz, 1H); 3.99 (br s, 1H); 3.78 (br s, 1H); 3.37 (br s, 3H, minor rotamer); 3.26 (m, 1H); 3.07 (s, 3H, major rotamer); 2.77 (s, 6H); 2.86-2.60 (m, 4H); 1.6-1.3 (m, 6H); 1.35 (d, *J* = 7 Hz, 6H).

Preparation of Examples BN and BO

[0374]

Scheme 57



I. Cmpd. 8/EDC/HOBt/DIPEA/THF; II. TFA, 1M NaOH.

Example BP

[0375] Example **BN** was prepared in a similar fashion to Example **BK** using Compound 112 (0.78 mmol) and Compound **8** (0.60 mmol) to produce 0.227 g (50%) of Compound **BN** as colorless film. (*m/z* 763.3 $(M+H)^+$).

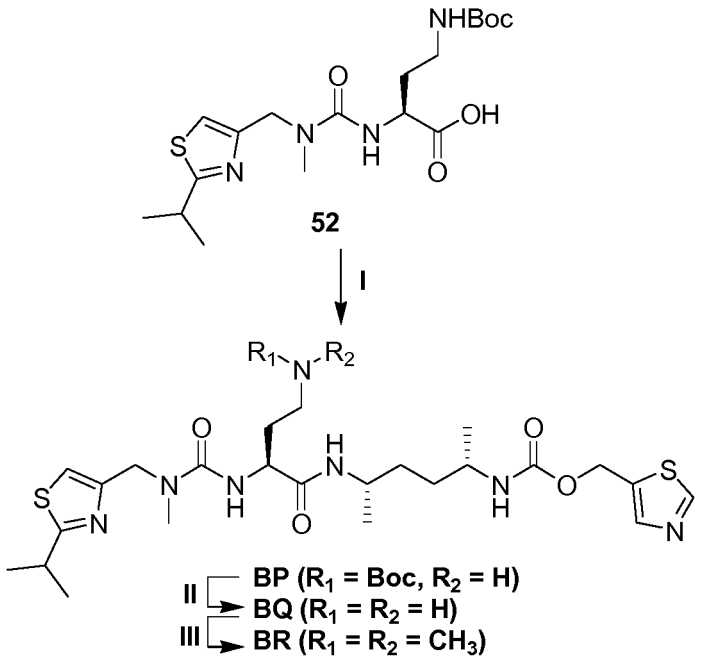
Example BO

[0376] Example **BO** was prepared in a similar fashion to Example **AM** using Example **BN** (0.29 mmol) to produce 0.149 g (72%) of Example **BO** as an amorphous white solid. (*m/z* 707.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.82 (s, 1H); 7.84 (s, 1H); 7.26-7.03 (m, 11H); 6.99 (s, 1H); 6.69 (d, *J* = 9.6, 1H); 6.42 (br s, 1H); 5.47 (br d, *J* = 8.7 Hz, 1H); 5.27 (AB d, *J* = 13 Hz, 1H); 5.22 (AB d, *J* = 13 Hz, 1H); 4.55 (AB d, *J* = 16 Hz, 1H); 4.43 (AB d, *J* = 16 Hz, 1H); 4.18 (m, 1H); 4.00 (m, 2H); 3.72 (br s, 1H); 2.25 (m, 1H); 2.99 (s, 3H); 2.84-2.60 (m, 3H); 2.54-2.42 (m, 1H); 1.64-1.12 (m, 4H); 1.37 (d, *J* = 7 Hz, 6H); 1.11 (d, *J* = 6 Hz, 3H).

Preparation of Examples BP-BR

[0377]

Scheme 58



I. Cmpd. 78/EDC/HOBt/DIPEA/THF; II. 4M HCl/dioxane; III. HCHO, $NaHB(OAc)_3$, MeOH

Example BP

[0378] Example **BP** was prepared in a similar fashion to Example **BK** using Compound 52 (0.22 mmol) and Compound **78** (0.20 mmol) to produce 0.091 g (71%) of Example **BP** as colorless film (*m/z* 654.2 $(M+H)^+$).

Example BO

[0379] Example **BQ** (0.14 mmol) was treated with 4M HCl in dioxane (2 mL) to produce a white precipitate within 5 min. The solvents were removed, and the solid was taken up in MeOH. Concentration *in vacuo* afforded 0.083 g (99%) of the HCl salt of Example **BQ** as a colorless film (*m/z* 554.1 $(M+H)^+$; ^{1}H-NMR (CD_3OD, 300 MHz): 10.03 (s, 1H); 8.41 (s, 1H); 7.81 (s, 1H); 5.48 (s, 2H, minor rotamer); 5.35 (s, 2H, major rotamer); 4.74 (s, 2H); 4.34 (br s, 1H); 3.90 (br s, 1H); 3.78-3.54 (m, 2H); 3.20-2.98 (m, 5H); 2.20 (br s, 1H); 2.07 (br s, 1H); 1.60-1.4 (m, 10H); 1.12 (m, 6H).

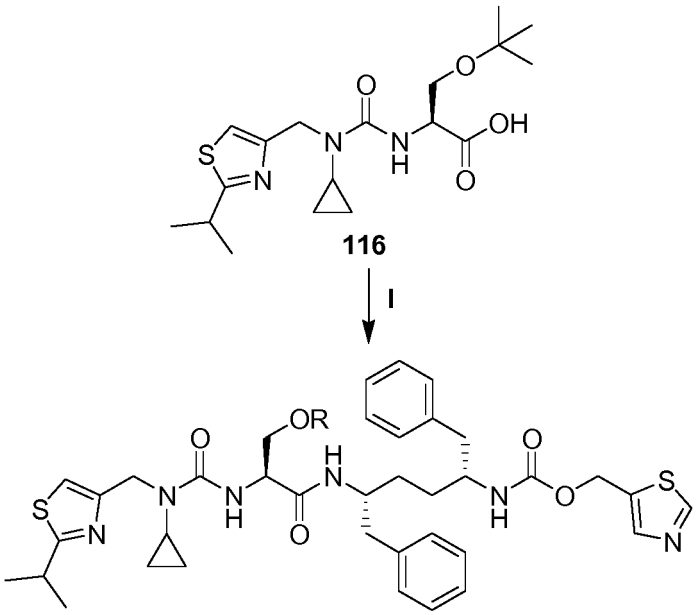
Example BR

[0380] Example **BQ** (0.11 mmol) was taken up in MeOH (1.5 mL). Formaldehyde (37% in H_2O, 13.4 mmol) was added and aged 10 min. $NaHB(OAc)_3$ (0.324 mmol) was added, and the reaction mixture was allowed to age at room temperature overnight. More formaldehyde (13.4 mmol) and $NaHB(OAc)_3$ (0.324 mmol) were added and allowed to age an additional 6 h at room temperature. The solvents were removed *in vacuo* and the product was isolated by preparatory HPLC to produce 0.058 g (77%) of the TFA salt of Example **BR** as an amorphous solid. *m/z* 582.3 $(M+H)^+$; ^{1}H-NMR (CD_3OD, 300 MHz): 9.07 (s, 1H); 7.91 (s, 1H); 7.25 (s, 1H); 5.47 (s, 2H, minor rotamer); 5.28 (s, 2H, major rotamer); 4.59 (AB d, *J* = 16 Hz, 1H); 4.53 (AB d, *J* =16 Hz, 1H); 4.31 (dd, *J* = 9.2, 5 Hz, 1H); 3.88 (m, 1H); 3.59 (m, 1H); 3.32 (m, 1H); 3.20 (m, 2H); 2.98 (s, 3H); 2.89 (br s, 6H); 2.23 (m, 1H); 2.00 (m, 1H); 1.44 (m, 4H); 1.37 (d, *J* = 7 Hz, 6H); 1.10 (m, 6H).

Preparation of Examples BS and BT

[0381]

Scheme 59



I. Cmpd. 8/EDC/HOBt/DIPEA/THF; II. TFA, 1M NaOH.

Compound 116

[0382] Compound **116** was prepared in a similar fashion to Compound **75** using Compound **4** (0.76 mmol) and Compound **47** (0.64 mmol) to produce 0.218 g (90%) of Compound **116** as a foamy white solid (*m*/*z* 384.1 $(M+H)^+$).

Example BS

[0383] Example **BS** was prepared in a similar fashion to Example **BK** using Compound **116** (0.28 mmol) and Compound **8** (0.25 mmol) to produce 0.139 g (72%) of Example **BS** as a colorless film (*m*/*z* 775.3 $(M+H)^+$).

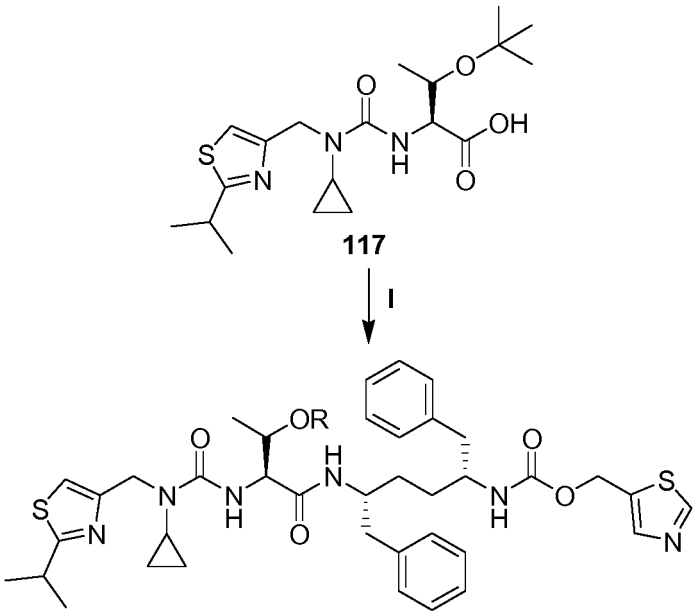
Example BT

[0384] Example **BT** was prepared in a similar fashion to Example **AM** using Example **BU** (0.18 mmol) to produce 0.080 g (62%) of Example **BT** as an amorphous white solid. *m*/*z* 719.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.79 (s, 1H); 7.82 (s, 1H); 7.27-7.0 (m, 10H); 6.98-6.82 (m, 1H); 6.85 (s, 1H); 6.44 (br s, 1H); 5.30 (s, 2H, minor rotamer); 5.22 (s, 2H, major rotamer); 5.04 (br s, 1H); 4.62 (AB d, *J* = 15 Hz, 1H); 4.54 (AB d, *J* =15 Hz, 1H); 4.27 (br s, 1H); 4.11 (br s, 1H); 3.97 (br d, *J* = 10 Hz, 1H); 3.82, br s, 1H); 3.57 (br s, 1H); 3.40-3.10 (m, 2H); 2.80-2.60 (m, 4H); 2.55 (m, 1H); 1.54 (m, 2H); 1.46-1.30 (m, 2H); 1.35 (d, *J* = 7 Hz, 6H); 0.94-0.72 (m, 4H).

Preparation of Examples BU and BV

[0385]

Scheme 60



I. Cmpd. 8/EDC/HOBt/DIPEA/THF; II. TFA, 1M NaOH.

Compound 117

[0386] Compound **117** was prepared in a similar fashion to Compound **13d** except that Compound **4** (1.5 mmol) and the ***L***-enantiomer of Compound **10d** (1.15 mmol) were used to ultimately produce 0.328 g (88%) of Compound **190** as a foamy white solid (*m*/*z* 398.1 $(M+H)^+$).

Example BU

[0387] Example **BU** was prepared in a similar fashion to Example **AL** using Compound **117** (0.33 mmol) and Compound **8** (0.30 mmol) to produce 0.196 g (84%) of Example **BU** as an amorphous white solid (*m*/*z* 789.3 $(M+H)^+$).

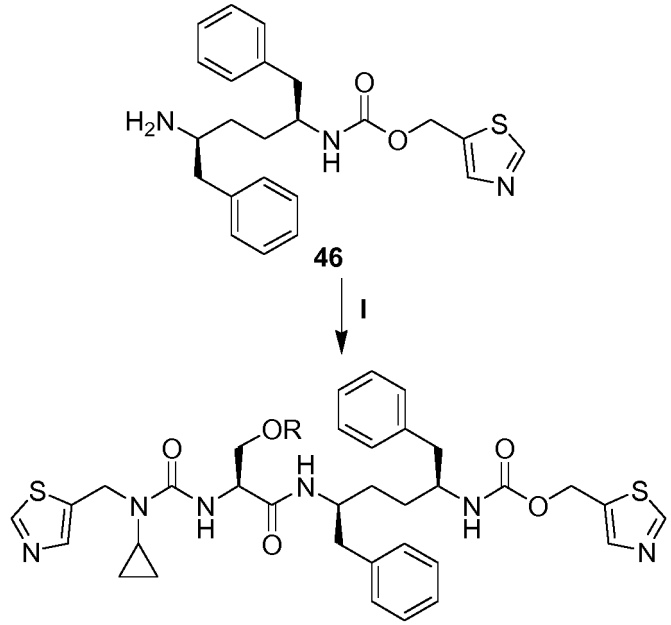
Example BV

[0388] Example **BV** was prepared in a similar fashion to Example **AM** using Example **BU** (0.29 mmol) to produce 0.140 g (77%) of Example **BV** as an amorphous white solid. *m*/*z* 733.3 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.80 (s, 1H); 7.84 (s, 1H); 7.27-7.10 (m, 10H); 6.70-6.10 (m, 1H); 6.86 (s, 1H); 6.20 (br d, *J* = 7 Hz, 1H); 5.24 (s, 2H); 4.81 (br d, *J* = 7 Hz, 1H); 4.82 (s, 2H); 4.34 (br d, *J* = 7 Hz, 1H); 4.16 (br s, 1H); 4.07 (br d, *J* = 6 Hz, 1H); 3.86 (br s, 1H); 3.38 (br s, 1H); 2.69 (m, 6H); 1.62-1.50 (m, 2H); 1.50-1.34 (m, 2H); 1.38 (m, 6H); 1.13 (d, *J* = 6 Hz, 3H); 0.98-0.76 (m,4H).

Preparation of Examples BW and BX

[0389]

Scheme 61



I Cmpd. 75/EDC/HOBt/DIPEA/THF; II. TFA, 1M NaOH.

Example BW

[0390] Example **BW** was prepared in a similar fashion to Example **BK** using Compound **75** (0.27 mmol) and Compound **46** (0.24 mmol) to provide 0.154 g (86%) of Example **BW** as an amorphous white solid (*m/z* 733.3 $(M+H)^+$).

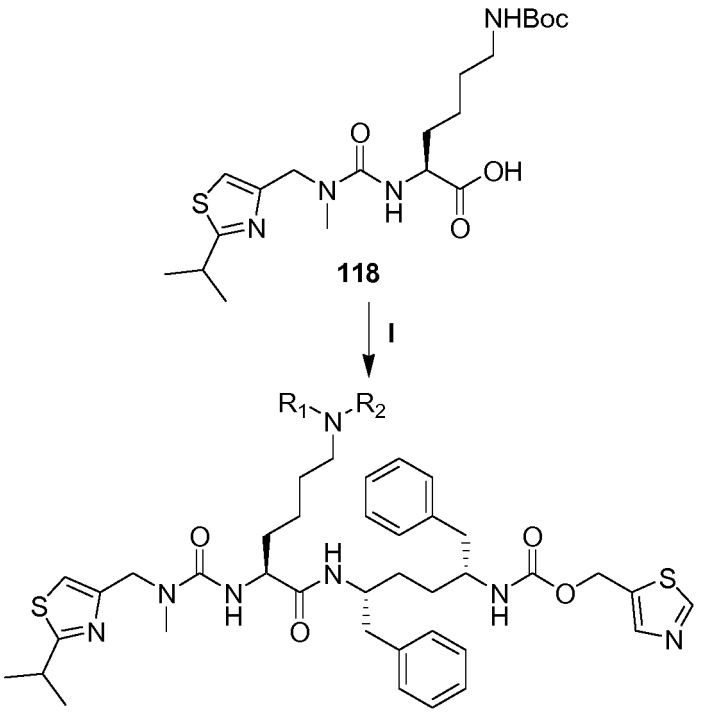
Example BX

[0391] Example **BX** was prepared in a similar fashion to Example **AM** using Example **BW** (0.21 mmol) to provide 0.091 g (98%) of the TFA salt of Example **BX** as an amorphous white solid. *m/z* 677.5 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.83 (s, 1H); 8.77 (s, 1H); 7.84 (s, 1H); 7.77 (s, 1H); 7.27-7.00 (m, 10H); 6.62 (d, *J* = 9 Hz, 1H); 6.44 (d, *J* = 6 Hz, 1H); 5.35 (d, *J* = 10 Hz, 1H); 5.24 (s, 2H); 4.69 (AB d, *J* = 15 Hz, 1H); 4.62 (AB d, *J* = 16 Hz, 1H); 4.14 (br m, 2H); 3.96-3.78 (m, 2H); 3.51 (dd, *J* = 11, 4.5 Hz, 1H); 3.38 (br s, 1H); 2.82-2.58 (m, 4H); 2.41 (m, 1H); 1.70-1.24 (m, 4H); 1.20-0.88 (m, 2H); 0.88-0.54 (m, 2H).

Preparation of Examples BY and BZ

[0392]

Scheme 62



I. Cmpd. 8/EDC/HOBt/DIPEA/THF; II. 4M HCl/dioxane.

Compound 118

[0393] Compound **118** was prepared in a similar fashion to Compound **104** except that Compound **115** (0.40 mmol) was used instead of Compound **102,** which was reacted with Compound **9** (0.48 mmol) to ultimately provide 0.075 g (89%) of Compound **118** as a foamy white solid (*m*/*z* 443.4 $(M+H)^+$).

Example BY

[0394] Example **BY** was prepared in a similar fashion to Example **BM** using Compound **118** (0.17 mmol) and Compound **8** (0.15 mmol) to produce 0.079 g (62%) of Example **BY** as an amorphous white solid (*m*/*z* 834.3 $(M+H)^+$).

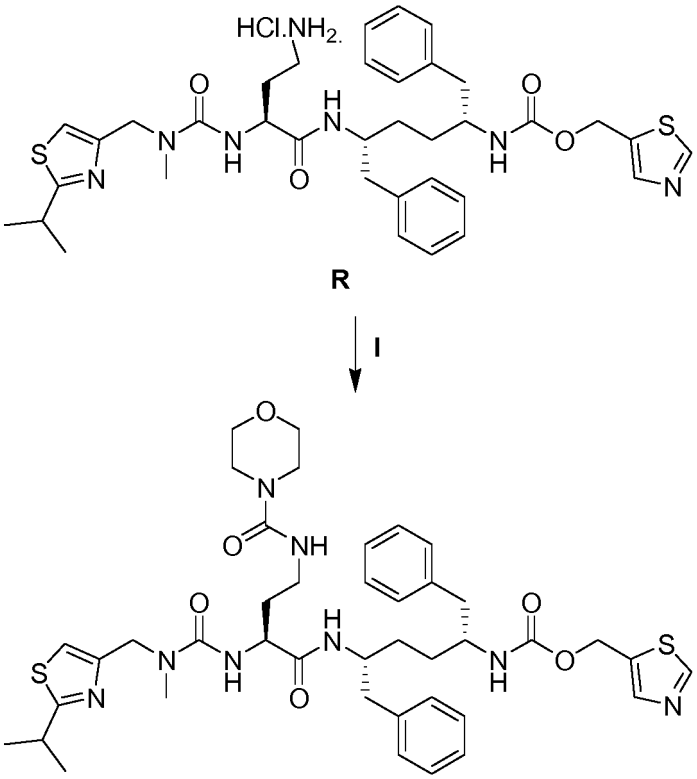
Example BZ

[0395] Example **BZ** was prepared in a similar fashion to Example **BQ** using Example **BY** (0.095 mmol) to provide 0.082 g (99%) of the HCl salt of Example **BZ** as an amorphous white solid *m*/*z* 734.2 $(M+H)^+$; ^{1}H-NMR (DMSO-d_6, 300 MHz): 8.08 (s, 1H); 7.86 (br m, 3H); 7.58 (d, *J* = 9 Hz, 1H); 7.25-7.00 (m, 11H); 6.32 (br s, 1H); 5.16 (s, 2H); 4.99 (br m, 4H); 4.48 (AB d, *J* = 15 Hz, 1H); 4.43 (AB d, *J* = 15 Hz, 1H); 4.02 (m, 1H); 3.89 (m, 1H); 3.63 (m, 1H); 3.22 (hep, *J* = 7 Hz, 1H); 2.87 (s, 3H); 2.76-2.56 (m, 4H); 1.58-1.15 (m, 10H); 1.29 (d, *J* = 7 Hz, 6H).

Preparation of Example CA

[0396]

Scheme 63



I. 4-morpholinecarbonyl chloride, DIPEA, DCM.

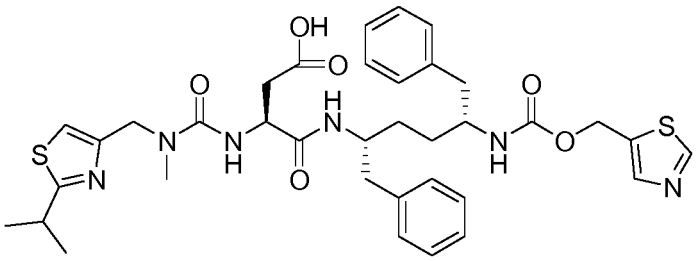
Example CA

[0397] Example **R** (0.11 mmol) was diluted in DCM (1 mL) and treated with 4-morpholinecarbonyl chloride (0.13 mmol) and DIPEA (0.16 mmol). After 2 h, volatiles were removed *in vacuo* and the residue was purified by column chromatography on SiO_2 (0-20% MeOH/DCM) to afford 0.068 g (76%) of Example **CA** as an amorphous white solid *m/z* 819.1 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.82 (s, 1H); 7.85 (s, 1H); 7.27-7.07 (m, 12H); 6.94 (s, 1H); 6.26 (br s, 1H); 5.73 (d, *J* = 8 Hz, 1H); 5.28 (AB d, *J* =13 Hz, 1H); 5.22 (AB d, *J* =13 Hz, 1H); 4.50 (AB d, *J* = 16 Hz, 1H); 4.44 (AB d, *J* = 16 Hz, 1H); 4.17 (m, 1H); 3.98 (br s, 1H) 3.76 (br s, 1H); 3.68 (br s, 1H); 3.60 (m, 4H); 3.40 (m, 2H), 3.32 (m, 4H); 2.97 (s, 3H); 2.87 (dd, *J* = 13, 5 Hz, 2H); 2.73, (m, 2H); 2.57 (m, 2H); 1.79 (m, 2H); 1.60-1.20 (m, 6H); 1.37 (d, *J* = 7 Hz, 6H).

Preparation of Compound CB

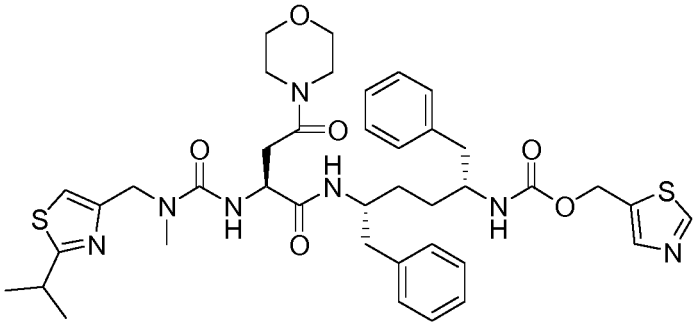
[0398]

Scheme 64



AF

I



CB

I. morpholine, EDC, HOBt, THF.

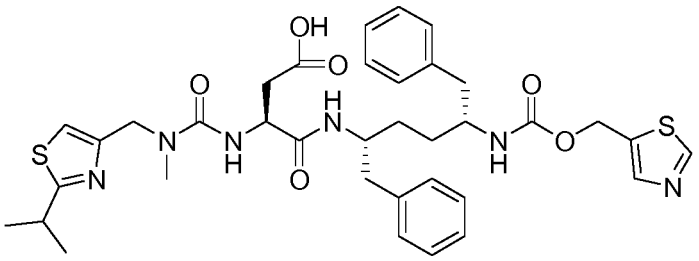
Example CB

[0399] Example **AF** (0.15 mmol) was diluted in THF (1 mL) and treated with morpholine (0.61 mmol), HOBt (0.18 mmol) and finally EDC (0.18 mmol). The reaction mixture was allowed to age overnight. The reaction mixture was then diluted in EtOAc and sat. Na_2CO_3. The aqueous layer was extracted with EtOAc and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified via preparatory HPLC to provide 0.024 g (20%) of Example **CB** as an amorphous white solid. *m/z* 790.4 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.81 (s, 1H); 7.84 (s, 1H); 7.27-7.10 (m, 10H); 6.96 (s, 1H); 6.78 (d, *J* = 8 Hz, 1H); 6.67 (s, 1H); 5.36 (d, *J* = 9 Hz, 1H); 5.27 (AB d, *J* = 13 Hz, 1H); 5.20 (AB d, *J* = 13 Hz, 1H); 4.59 (s, 1H); 4.51 (s, 2H); 4.02 (m, 1H); 3.80-3.30 (m, 10H); 2.98 (s, 3H); 2.90-2.45 (m, 6H); 1.52 (m, 2H); 1.39 (d, *J* = 7 Hz, 6H); 1.32 (m, 2H).

Preparation of Compound CC

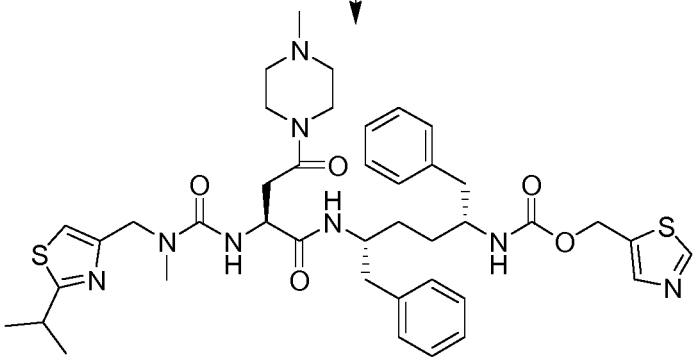
[0400]

Scheme 65



AF

I



CC

I. N-methylpiperazine, EDC, HOBt, DIPEA,THF.

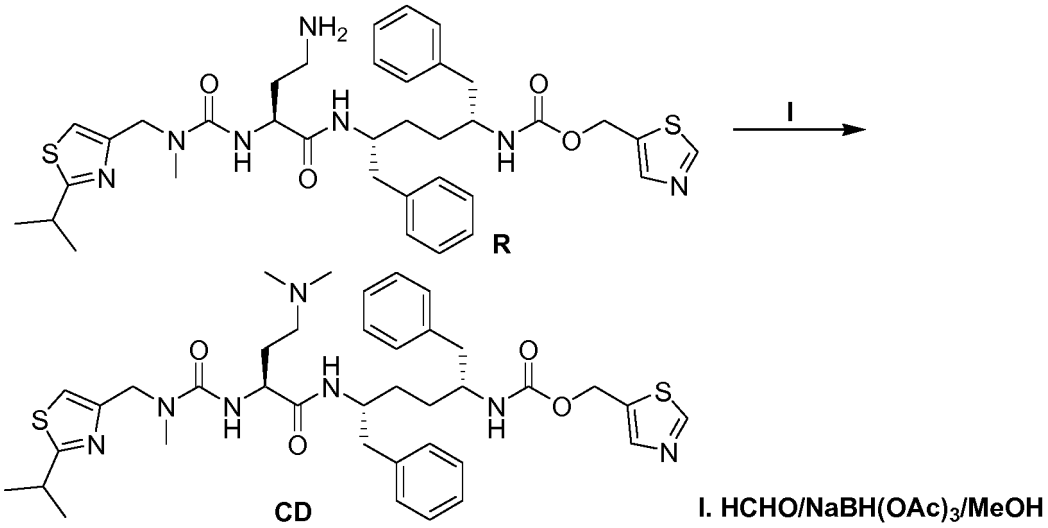
Example CC

[0401] Example **CC** was prepared in a similar fashion to Example **CB** except that N-methylpiperazine (0.16 mmol) was reacted with Compound **AF** (0.10 mmol) instead of morpholine and DIPEA (0.19 mmol) was added to produce 0.009 g (11%) of Example **CC** as an amorphous white solid *m/z* 803.4 $(M+H)^+$; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.80 (s, 1H); 7.84 (s, 1H); 7.27-7.10 (m, 11H); 6.91 (s, 1H); 6.78 (m, 2H); 5.27 (AB d, *J* =13 Hz, 1H); 5.21 (AB d, *J* =13 Hz, 1H); 4.59 (m, 1H); 4.49 (AB d, *J* = 16 Hz, 4.44 (AB d, *J* =16 Hz, 1H); 4.01 (m, 1H); 3.90-3.40 (m, 4H); 3.27 (hep, *J* = 7 Hz, 1H); 3.10-2.90 (m, 1H); 2.97 (s, 3H); 2.90-2.30 (m, 11H); 1.60-1.25 (m, 6H); 1.37 (d, *J* = 7 Hz, 6H).

Preparation of Example CD

[0402]

Scheme 66



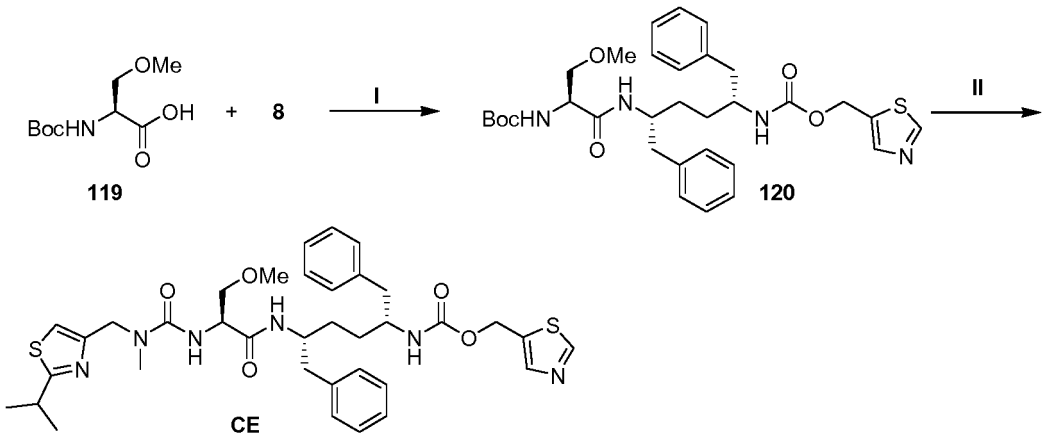
Example CD

[0403] To a solution of Example **R** (30.5 mg, 0.043 mmol) in methanol (1.5 mL) was added formaldehyde (1 mL, 37% in H_2O). After stirring for 10 minutes, $NaBH(OAc)_3$ (49 mg, 0.23 mmol) was added and the resulting mixture was stirred for 10 h. The reaction was monitored with LC/MS. When LC/MS indicated the absence of starting material Example **R,** the reaction mixture was evaporated to dryness, and filtered through a cotton plug. The crude product was then purified through CombiFlash (10% $MeOH/CH_2Cl_2$) to give 29.7 mg of Example **CD** ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.78 (s, 1H); 7.83 (s, 1H); 7.12-7.22 (m, 10H); 6.85 (s, 1H); 5.83 (d, 1H, J = 8.5 Hz), 5.23 (d_{AB}, 2H, J = 13.1 Hz); 4.49 (d_{AB}, 2H, J = 16.5 Hz); 4.29 (m, 1H); 4.15 (m, 1H); 3.75 (m, 1H); 3.30 (m, 1H); 2.93 (s, 3H); 2.87 (dd, 1H, J1 = 5.5 Hz, J2 = 13.5 Hz); 2.72 (m, 2H); 2.66 (dd, J1 = 7.3 Hz, J2 = 13.3 Hz), 2.47 (br s, 1H), 2.36 (br s, 1H), 2.23 (s, 6H), 1.91 (m, 2H), 1.56 (m, 2H), 1.40 (m, 2H), 1.40 (d, 6H, J = 6.8 Hz). *m/z* 734 (M+H)+; 756 $(M+Na)^+$;

Preparation of Example CE

[0404]

Scheme 67



Compound 119

[0405] Compound **119** is commercially available from Aldrich, and was used as received.

Compound 120

[0406] A mixture of Compound **119** (200 mg, 0.91 mmol), Compound **8** (373.7 mg, 0.91 mmol), EDC (212 mg, 1.37 mmol), HOBt (160.3 mg, 1.19 mmol) and iPr_2NEt (794.7 μL, 4.56 mmol) in THF was stirred for 10 h at room temperature. The mixture was then evaporated to a small volume and purified by CombiFlash (eluted with 1 to 10 % $MeOH/CH_2Cl_2$). The fractions containing the target Compounds were collected and re-purified by CombiFlash (40-100% EtOAc/hexanes) to give 449 mg of Compound **120** as oil. (*m/z* 611.0 $(M+H)^+$).

Example CE

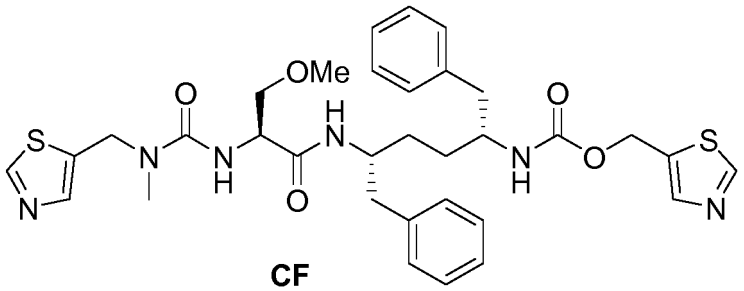
[0407] Compound **120** (449 mg, 0.74 mmol) was treated with HCl/dioxane (3 mL). The resulting mixture was evaporated to dryness and lyophilized to provide 373.6 mg of a white solid.

[0408] To a solution of the above white compound (52.5 mg, 0.096 mmol) in CH_2Cl_2 (10 mL) was added Compound **9** (19.8 mg, 0.096 mmol), CDI (15.6 mg, 0.096 mmol) followed by iPr_2NEt (33.4 μL, 0.192 mmol). The mixture was stirred for 20 h before it was evaporated to dryness. The mixture was added CH_2Cl_2, then filtered through a cotton plug. The filtrate was evaporated to dryness and purified with CombiFlash. The fractions with Example **CE** was collected and re-purified on the TLC to give 15.1 mg of Example **CE**. ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.79 (s, 1H); 7.82 (s, 1H); 7.09-7.27 (m, 10H), 6.94 (s, 1H); 6.25 (d, 2H, J = 8.7 Hz); 5.23 (s, 2H); 5.17 (br s, 1H); 4.43 (d_{AB}, 2H, J = 16.5 Hz); 4.29 (m, 1H); 4.13 (m, 1H), 3.76 (m, 2H); 3.48 (m, 1H); 3.29 (s, 3H); 3.25 (m, 1H), 2.94 (s, 3H), 2.65-2.82 (m, 4H), 1.75 (m, 2H), 1.54 (m, 2H), 1.39 (d, 5H, J = 6.9 Hz). *m/z* 707 $(M+H)^+$; 729 $(M+Na)^+$.

Preparation of Example CF

[0409]

Scheme 68



CF

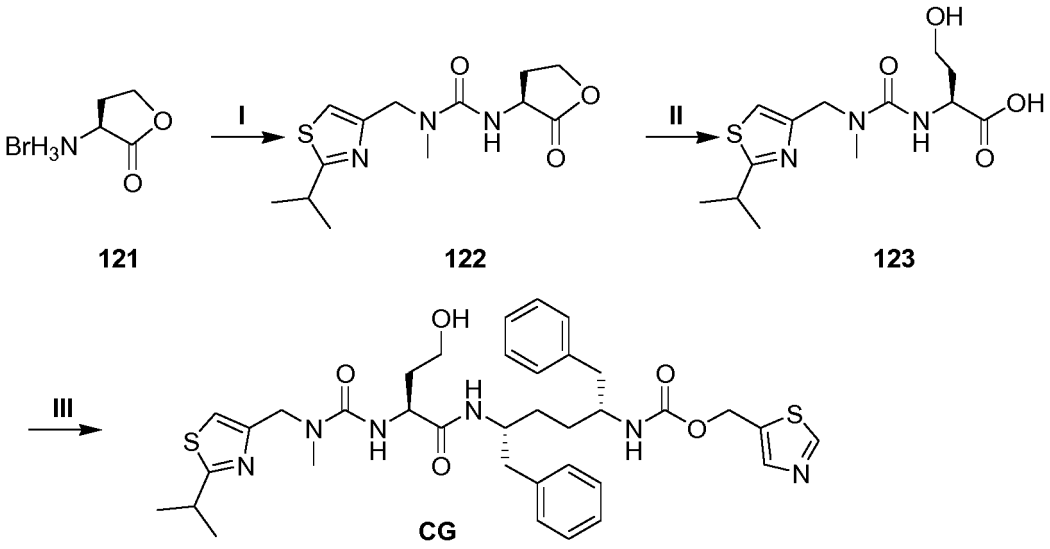
Example CF

[0410] Example **CF** was prepared using the same method as Example **CE,** except that Compound **9** was replaced with Compound **68.** ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.79 (s, 1H); 8.74 (s, 1H), 7.81 (s, 1H), 7.73 (s, 1H); 7.12-7.27 (m, 10H); 6.15 (d, 1H, J = 8.7 Hz), 5.39 (d, 1H, J = 6.8 Hz); 5.21 (s, 2H), 5.06 (d, J = 9.1 Hz, 1H); 4.64 (d_{AB}, 2H, J = 15.5 Hz); 4.28 (m, 1H); 4.134 (m, 1H), 3.79 (m, 1H), 3.70 (m, 1H); 3.34 (m, 1H); 3.28 (s, 3H); 2.87 (s, 3H); 2.72 (m, 4H); 1.57 (m, 2H); 1.50 (m, 2H). (*m/z* 665.2 $(M+H)^+$; 687.3 $(M+Na)^+$.

Preparation of Compound CG

[0411]

Scheme 69



I. a. CDI, DIPEA, MeCN; b. compound 9, MeCN. II. 1M LiOH, THF.
III. EDCI, HOBt, iPr2NEt, compound 8

Compound 121

[0412] Compound **121** is commercially available from Aldrich, and was used as received.

Compound 122

[0413] To a suspension of Compound **121** (2.05 g, 11.3 mmol) in CH_2Cl_2 (40 mL) was added. iPr_2NEt (5.87 mL, 33.9 mmol) followed by CDI (1.86 g, 11.3 mmol). The resulting mixture was stirred at room temperature for 6 h, then Compound **9** (2.33g, 11.3 mmol) was added. The resulting mixture was stirred for another 10 h before it was evaporated to dryness. The mixture was re-dissolved in CH_2Cl_2 and the solid was removed by filtration. The filtrate was evaporated to dryness and purified by CombiFlash (eluted with 20-80% EtOAc/hexanes) to give 3.2 g of Compound **207** as a pale yellow oil. *m/z* 298.0 $(M+H)^+$.

Compound 123

[0414] To a solution of Compound **122** (3.2g, 10.8 mmol) in THF (100 mL) was added freshly prepared 1M LiOH (10.8 mmol). The biphasic reaction was stirred vigorously at room temperature for 16 h before being quenched with 1M HCl. The pH of the mixture was adjusted to 2.5-3, and then evaporated to a small volume. The mixture was partitioned between CH_2Cl_2 and brine (50 mL), the aqueous layer was separated and extracted with CH_2Cl_2 twice. The combined CH_2Cl_2 layers were dried over anhydrous Na_2SO_4 and concentrated to give 3.37 g of Compound **123** a pale yellow oil that is used with further purification. *m/z* 316.0 $(M+H)^+$, 338 $(M+Na)^+$;

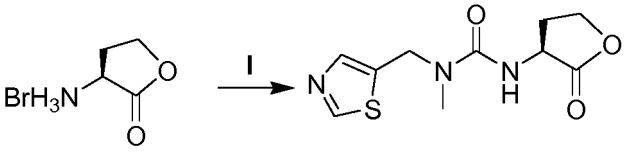
Example CG

[0415] Example **CG** was prepared following the same procedure for Example **C** instead that Compound **123** was used instead of Compound **7.** ^{1}H-NMR ($CDCl_3$, 500 MHz): 8.80 (s, 1H); 7.83 (s, 1H), 7.11-7.26 (m, 10H), 6.96 (s, 1H); 7.12-7.27 (m, 10H); 6.52 (br s, 1H), 6.40 (br s, 1H), 5.23 (s, 2H), 5.20 (m, 1H), 4.44 (d_{AB}, 2H, J =15.5 Hz), 4.39 (m, 1H), 4.11 (m, 1H), 3.80 (m, 1H), 3.61 (m, 2H), 3.28 (sep, 1H, J = 7.0 Hz); 2.94 (s, 3H), 2.79 (dd, 1H, J1 = 6.1 Hz, J2 = 13.4 Hz); 2.71 (m, 3H), 1.93 (m, 1H), 1.71 (m, 1H), 1.54 (m, 1H), 1.38 (d, 6H, J = 7.0 Hz) 1.37 (m, 1H). (: $)^+$; *m/z* 707.3 $(M+H)^+$), 729.2 $(M+Na)^+$.

Preparation of Compound 100

[0416]

Scheme 70



121 100

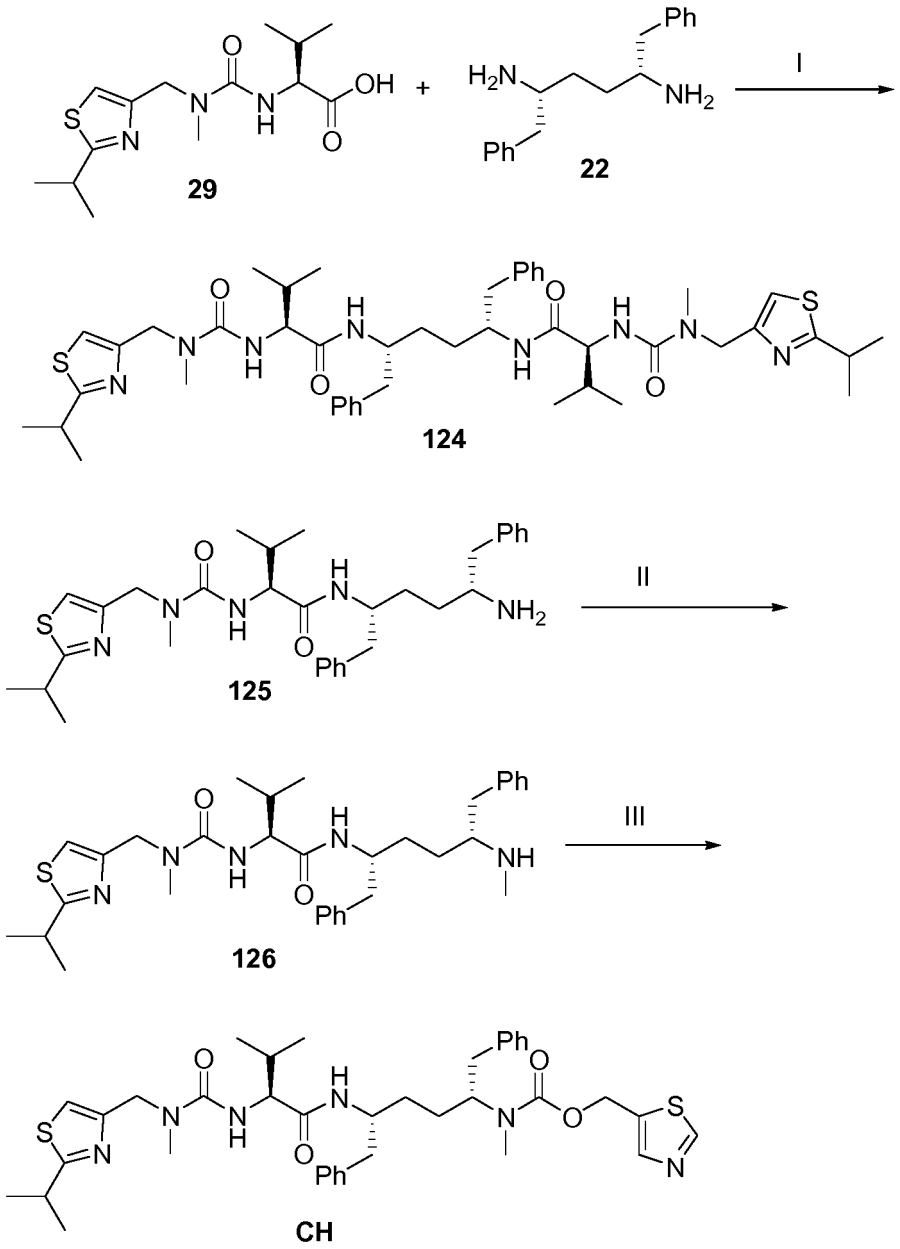
I. a. CDI, DIPEA, MeCN;

[0417] Compound **100** was prepared using the same method used to prepare Compound **122,** except that Compound **9** was replaced with Compound **68.**

Preparation of Example CH

[0418]

Scheme 71



I. EDCI/HOBt/iPr_2NEt/THF; II. HCHO/$NaBH(OAc)_3$/HOAc/CH_3CN;
III. Cmpd. 16/iPr_2NEt/CH_3CN

Compounds 124 and 125

[0419] To a solution of Compound **29** (135 mg, 0.43 mmol) and Compound **22** (116 mg, 0.43 mmol) in THF (5 mL) were added HOBt (70 mg, 0.52 mmol), EDC (94 μL, 0.52 mmol), and diisopropylethylamine (150 μL, 0.83 mmol). The mixture was stirred for 12 hours and concentrated. Purification by reverse HPLC gave Compound **124** (70 mg) and Compound **125** (120 mg). Compound **124:** ^{1}H-NMR ($CDCl_3$) b 7.2-7.1 (10 H, m), 7.0 (2 H, s), 6.45 (2 H, m), 6.15(2 H, m), 4.45 (4 H, s), 4.1 (2 H, m), 3.96 (2 H, m), 3.3 (2 H, m), 2.98 (6 H, s), 2.7 (4 H, m), 2.1 (2 H, m), 1.6-1.3 (16 H, m), 0.90 (12 H, m). m/z 859.3 $(M+H)^+$; Compound 125: m/z 564.3 $(M+H)^+$

Compound 126

[0420] To a solution of Compound **125** (120 mg, 0.21 mmol) in CH_3CN (1 mL) was added 37% formaldehyde solution (17 μL, 0.23 mmol), followed by HOAc (24 μl, 0.42 mmol). The mixture was stirred for 2 hours, and $NaBH(OAc)_3$ (140 mg, 0.63 mmol) was added. The mixture was stirred for 2 additional hours and diluted with EtOAc. The organic phase was washed with saturated Na_2CO_3 solution, water, and brine, and dried over Na_2SO_4. Concentration gave Compound **126,** which was used in the next step without further purification. m/z 578.3 $(M+H)^+$

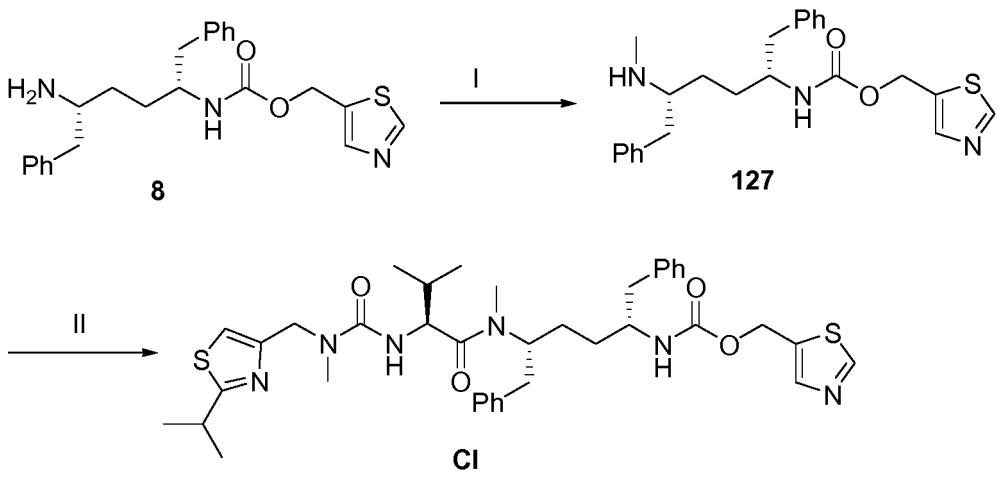
Example CH

[0421] Example **CH** (26 mg) was prepared following the procedure used to prepare Example **L,** except that Compound **126** was used instead of Compound **22.** ^{1}H-NMR (CDCl3) b 8.91 (1 H, m), 7.82 (1 H, m), 7.2-7.0 (11 H, m), 6.4 (1 H, m), 6.2 (1 H, m), 5.23-5.05 (2 H, m), 4.44 (2 H, s), 4.44 (1 H, m), 4.2 (1 H, m), 3.95 (1 H, m), 3.32 (1 H, m), 2.98 (3 H, s), 2.8-2.5 (7 H, m), 2.15 (1 H, m), 1.7-1.2 (10 H, m), 0.88 (6 H, m). m/z 719.3 $(M+H)^+$

Preparation of Example CI

[0422]

Scheme 72



I. $HCHO/NaBH(OAc)_3/HOAc/CH_3CN$; II. Cmpd. 29/EDCI/HOBt/iPr_2NEt/THF

Compound 127

[0423] Compound **127** (110 mg) was prepared following the procedure used to prepare Compound **126,** except that Compound **8** was used instead of Compound **125.** m/z 424.4 $(M+H)^+$

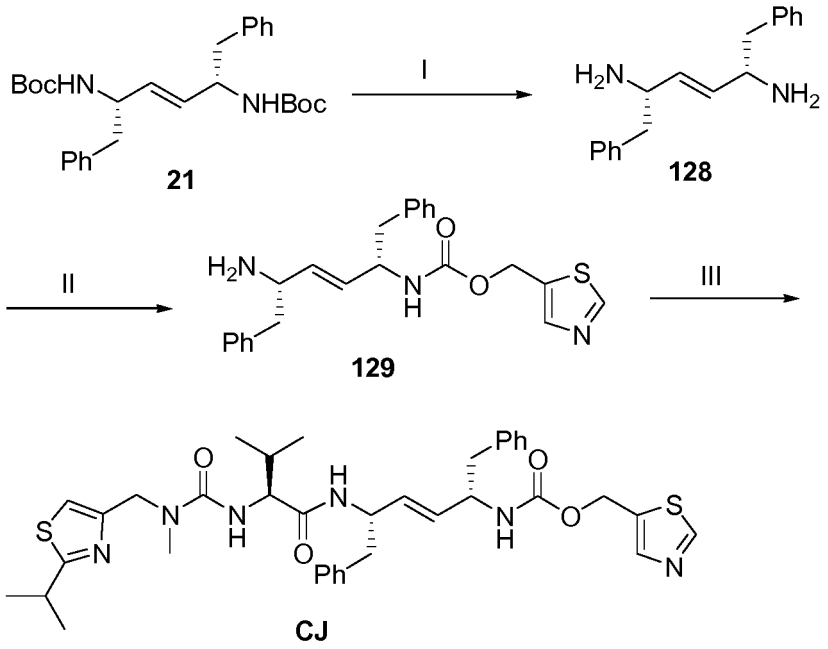
Example CI

[0424] Example **CI** (7 mg) was prepared following the procedure used to prepare Example C, except that Compounds **127** and **29** were used instead of Compounds 8 and 7. ^{1}H-NMR (CDCl3) δ 9.0 (1 H, s), 8.92 (1 H, s), 7.4-7.0 (11 H, m), 5.25 (2 H, m), 4.6-4.0 (5 H, m), 3.4 (1 H, m), 3.1-2.6 (10 H, m), 1.9 (1 H, m), 1.8 (10 H, m), 0.9 (6 H, m); m/z 719.2 $(M+H)^+$

Preparation of Compound CJ

[0425]

Scheme 73



I. a. TFA/CH_2Cl_2; b. Na_2CO_3; II. Cmpd. 16/iPr_2NEt/CH_3CN;
III. Cmpd. 29/EDCI/HOBt/iPr_2NEt/THF

Compound 128

[0426] To a solution of Compound **21** (100 mg) in dichloromethane (5 mL) was added TFA (1 mL). The mixture was stirred for 3 hours, and excess reagents were evaporated. The oil was diluted with EtOAc, and then was washed with saturated Na_2CO_3 solution (2x), water (2x), and brine, and dried over Na_2SO_4. Concentration gave Compound **128** (46 mg). m/z 267.1 $(M+H)^+$

Compound 129

[0427] Compound **129** (44 mg) was prepared following the procedure for Compound **8,** except that Compound **128** was used instead of Compound **22.** m/z 408.10 $(M+H)^+$

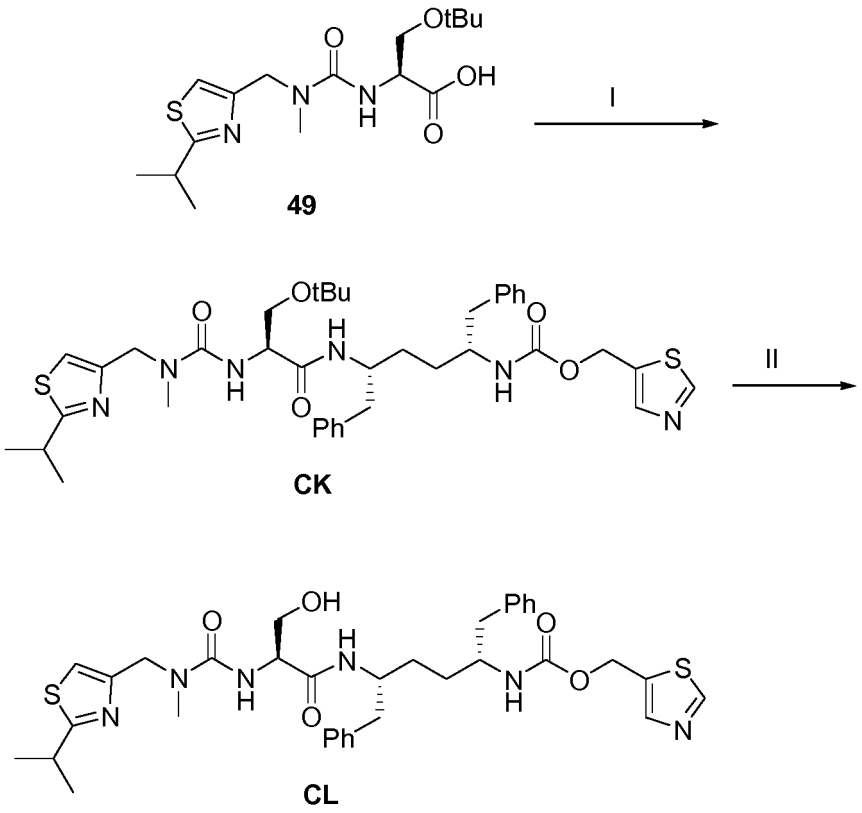
Example CJ

[0428] Example **CJ** (55 mg) was prepared following the procedure for Example C, except that Compounds **129** and **29** were used instead of Compounds **8** and **7**. ^{1}H-NMR (CDCl3) δ 8.81 (1 H, s), 7.85 (1 H, s), 7.2-7.0 (11 H, m), 6.4 (1 H, m), 6.12 (1 H, m), 5.44 (2 H, m), 5.26 (2 H, s), 4.85 (1 H, m), 4.70 (1 H, m), 4.4 (3 H, m), 4.06 (1 H, m), 3.25 (1 H, m), 2.98 (3 H, s), 2.78 (4 H, m), 2.21 (1 H, m), 1.38 (6 H, m), 0.88 (6 H, m); m/z 703.2 $(M+H)^+$

Preparation of Compounds CK and CL

[0429]

Scheme 74



I. Cmpd 8/EDC/HOBt; II. a. TFA; b. NaOH/THF

Example CK

[0430] Example **CK** (88 mg) was prepared following the procedure used to prepare Example **C,** except that Compound **49** was used instead of Compound **7.** m/z 749.2 $(M+H)^+$

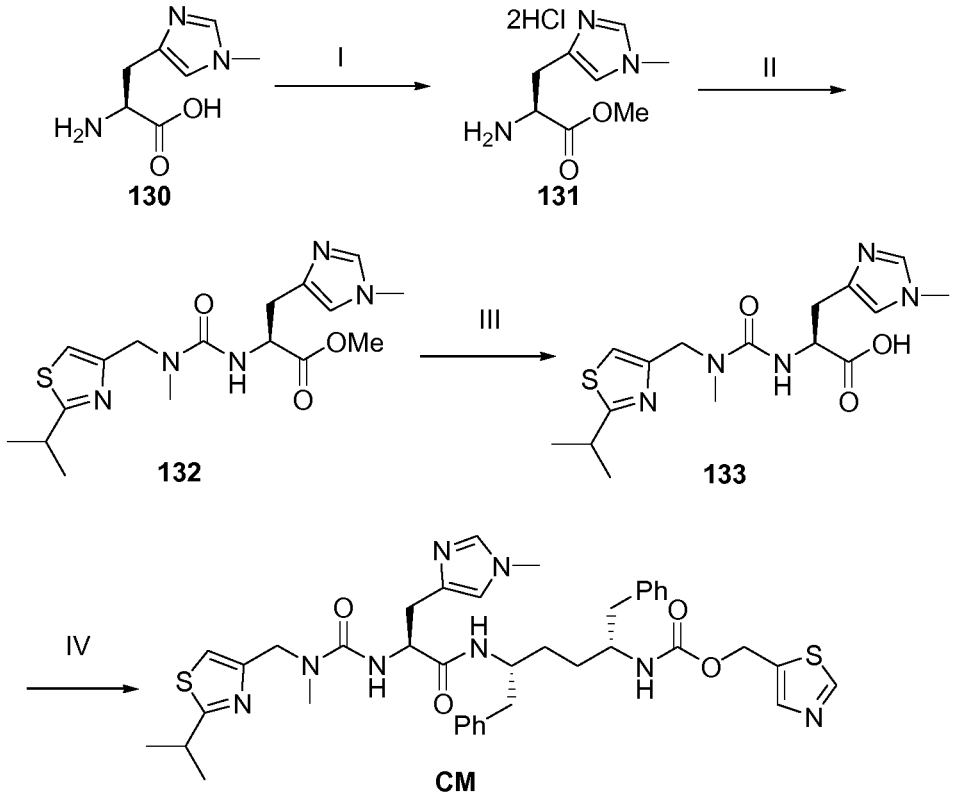
Example CL

[0431] A mixture of Example **CK** (85 mg) and TFA (5 mL) was stirred for 3 hours. Excess TFA was evaporated and the mixture was dried under high vacuum. The mixture was dissolved in THF (5 mL), and 1.0 N sodium hydroxide solution was added until the pH was 11. The solution was stirred for 10 minutes, and extracted with EtOAc. The organic phase was washed with water, brine, and dried over Na_2SO_4.
Concentration and purification by flash column chromatography (EtOAc) gave Example **CL** (66 mg). ^{1}H-NMR (CDCl3) b 8.81 (1 H, s), 7.84 (1 H, s), 7.30-6.96 (11 H, m), 5.22 (2 H, s), 4.90 (1 H, m), 4.45 (1 H, m), 4.35-4.0 (4 H, m), 3.8 (1 H, m), 3.6 (1 H, m), 3.21 (1 H, m), 2.95 (3 H, s), 2.8-2.6 (4 H, m), 2.0-1.4 (4 H, m), 1.25 (6H, m). m/z 693.2 $(M+H)^+$.

Preparation of Example CM

[0432]

Scheme 75



I. $SOCl_2$/MeOH; II. a. CDI/iPr_2NEt; b. Cmpd. 9; III.a. NaOH/THF/H_2O; b. HCl; IV. Cmpd. 8/EDC/HOBt;

Compound 130

[0433] Compound **130** is commercially available from (TCI), and was used as received.

Compound 131

[0434] To the solution of Compound **130** (510 mg, 3 mmol) in methanol (12 mL) at 0 ºC was added thionyl chloride (0.5 mL, 6.6 mmol), dropwise. The mixture was stirred at 0 ºC for 30 minutes and brought to reflux for 3 hours. Concentration gave Compound **131** as a white solid.

Compound 132

[0435] To a stirred solution of Compound **131** (3 mmol) and diisopropylethylamine (2 mL, 12 mmol) in dichloromethane (35 mL) was added CDI (486 mg, 3 mmol). The mixture was stirred for 12 hours. Compound **9** was added, and the mixture was stirred for 12 additional hours. Concentration and purification by flash column chromatography (CH_2Cl_2/iPrOH = 10/1) gave Compound **132** (414 mg). m/z 380.0 $(M+H)^+$

Compound 133

[0436] Compound **133** was prepared following the procedure for Compound **67,** except that Compound **132** was used instead of Compound **66.** m/z 364.0$(M-H)^-$

Example CM

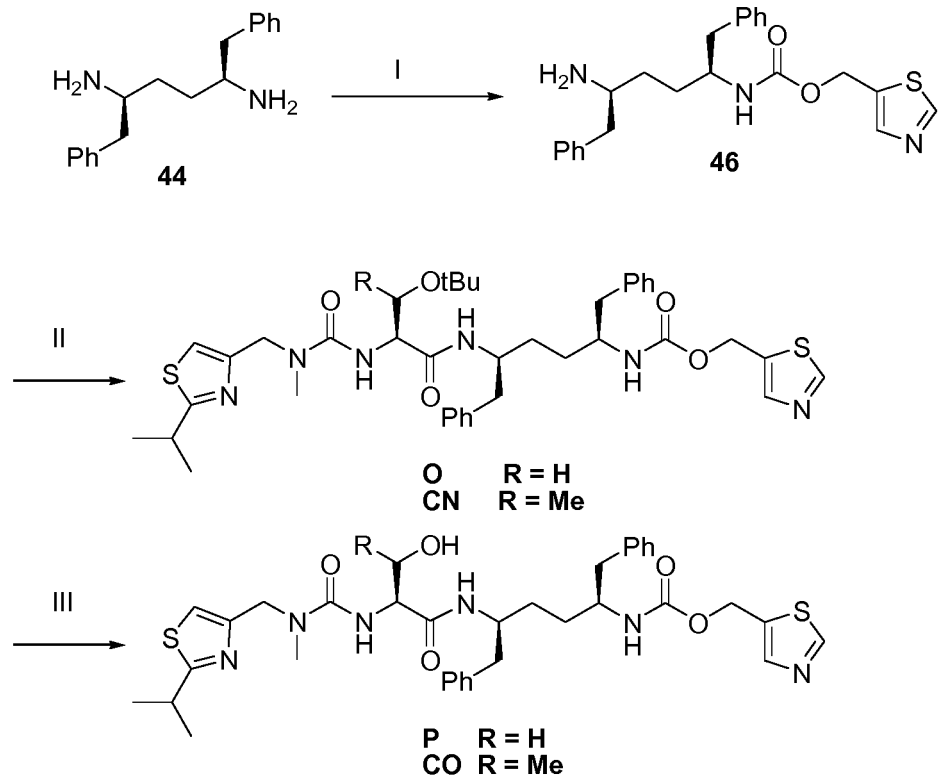
[0437] Example **CM** (600 mg) was prepared following the procedure for Example **C,** except Compound **133** was used instead of Compound **7.** ^{1}H-NMR (CDCl3) b 9.18 (1 H, s), 8.35 (1 H, s), 7.95 (1 H, s), 7.6 (1 H, m), 7.3-7.0 (11 H, m),

5.22 (2 H, m), 4.70 (1 H, m), 4.50 (2 H, m), 4.05 (1 H, m), 3.86 (3 H, s), 3.80 (2 H, m), 3.55 (1 H, m), 3.10 (1 H, m), 2.90 (3 H, s), 2.70 (4 H, m), 1.45 (10 H, m); m/z 757.3 $(M+H)^+$

Preparation of Examples O, P, CN, and CO

[0438]

Scheme 76



I. Cmpd. 16/iPr2NEt; II. Cmpd. 13d or Cmpd. 49/EDC/HOBt; III. a. TFA; b. NaOH/THF

Example O

[0439] Example **O** (17 mg) was prepared following the procedure for Example **C,** except Compounds **46** and **49** were used instead of Compounds **8** and **7.** m/z 749.3 $(M+H)^+$

Example CN

[0440] Example **CN** (22 mg) was prepared following the procedure used to prepare Example **C,** except Compounds **46** and **13e** were used instead of Compounds **8** and 7. m/z 763.2 $(M+H)^+$

Example P

[0441] Example **P** (12 mg) was prepared following the procedure used to prepare Example **CM,** except Example **O** was used instead of Example **CL.** ^{1}H-NMR ($CDCl_3$) b 8.76 (1 H, s), 7.79 (1 H, s), 7.25-6.9 (11 H, m), 6.51 (1 H, broad), 5.42 (1 H, m), 5.18 (2 H, m), 4.42 (2 H, m), 4.22 (1 H, m), 4.10 (1 H, m), 3.95 (1 H, m), 3.79 (1 H, m), 3.58 (1 H, m), 3.23 (1 H, m), 2.93 (3 H, s), 2.9-2.5 (4 H, m), 1.6-1.2 (10 H, m); m/z: 693.2 $(M+H)^+$.

Compound CO

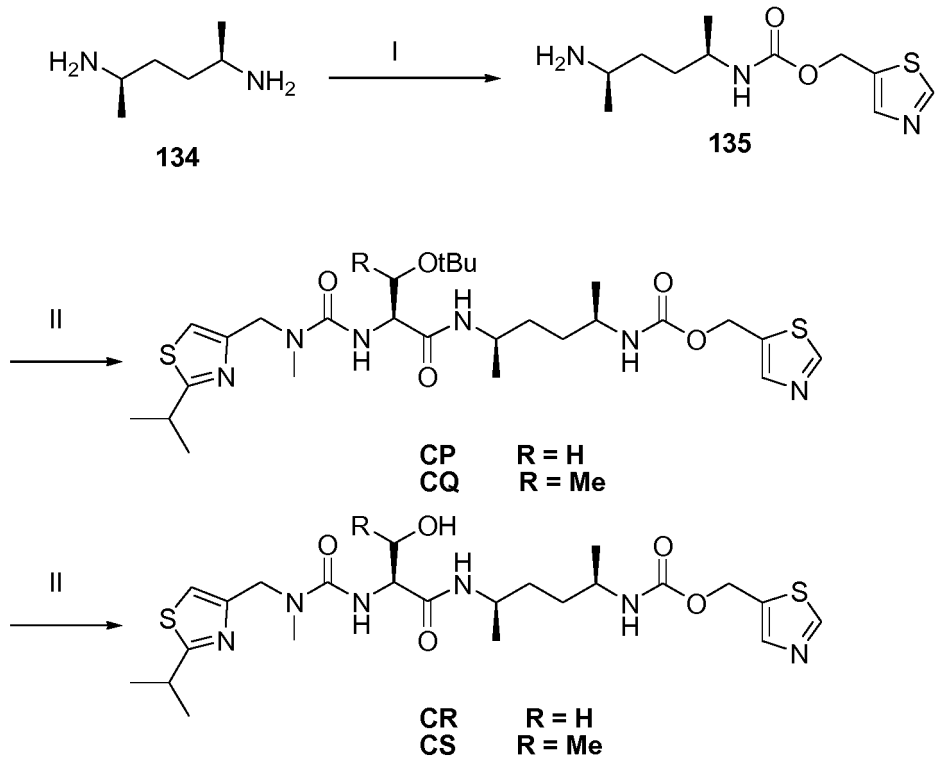
[0442] Example **CO** (13 mg) was prepared following the procedure used to prepare Example **CL,** except Example **CN**

was used instead of Compound **CK.** ^{1}H-NMR ($CDCl_3$) b 8.85 (1H, m), 7.88 (1 H, m), 7.3-7.0 (11 H, m), 6.55 (1 H, m), 6.24 (1 H, m), 5.45 (1 H, m), 5.23 (2 H, m), 4.6 (2 H, m), 4.2 (1 H, m), 4.0 (2 H, m), 3.7 (1 H, m), 3.5 (1 H, m), 3.02 (3 H, s), 2.70 (4 H, m), 1.6-1.0 (13 H, m); m/z: 707.3 $(M+H)^+$.

Preparation of Examples CP-CS

[0443]

Scheme 77



I. Cmpd. 16/iPr_2NEt; II. Cmpd. 13d or 49/EDC/HOBt; III. a. TFA; b. NaOH/THF

Compound 134

[0444] Compound **134** was prepared using procedure described for Compound **76,** except that CBZ-D-alaninol was used instead of CBZ-L-alaninol.

Compound 135

[0445] Compound **135** was prepared following the procedure used to prepare Compound **8**, except Compound **134** was used instead of Compound **22.**

Example CP

[0446] Example **CP** (12 mg) was prepared following the procedure used to prepare Example **C,** except Compounds **135** and **49** were used instead of Compounds **8** and **7.** m/z 597.2 $(M+H)^+$.

Example CO

[0447] Example **CQ** (11 mg) was prepared following the procedure used to prepare Example **C,** except Compounds **135** and **13d** were used instead of Compounds **8** and **7.** m/z 611.2 $(M+H)^+$.

Example CR

[0448] Example **CR** (7 mg) was prepared following the procedure used to prepare Example **P**, except that Example **CP** was used instead of Example **O**. ^{1}H-NMR ($CDCl_3$) δ 8.82 (1 H, s), 7.88 (1 H, s), 7.02 (1 H, s), 6.92 (1 H, m), 5.28 (2 H, s), 5.10 (1 H, m), 4.5 (2 H, m), 4.15 (2 H, m), 3.88 (1 H, m), 3.8-3.5 (2 H, m), 3.35 (1 H, m), 3.0 (3 H, s), 1.5-1.0 (16 H, m); m/z: 541.1 $(M+H)^+$.

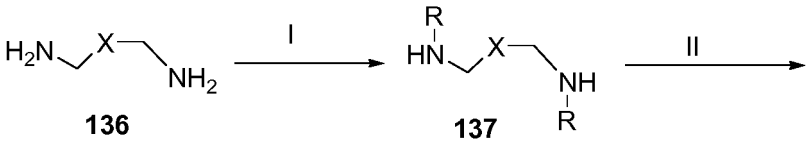
Example CS

[0449] Example **CS** (8 mg) was prepared following the procedure used to prepare Example **CO,** except that Example **CQ** was used instead of Example **CN.** ^{1}H-NMR ($CDCl_3$) δ 8.83 (1 H, s), 7.88 (1 H, s), 6.98 (1 H, s), 6.81 (1 H, m), 6.58 (1 H, m), 5.28 (2 H, s), 5.18 (1 H, m), 4.4-4.3 (2 H, m), 4.03 (1 H, m), 3.85 (1 H, m), 3.58 (2 H, m), 3.3 (1 H, m), 2.99 (3 H, s), 1.5-0.98 (19 H, m); m/z: 555.2 $(M+H)^+$.

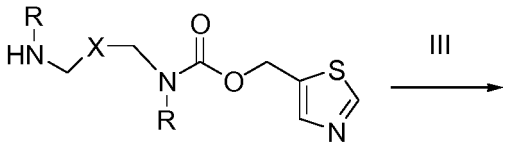
Preparation of Examples CT-CV

[0450]

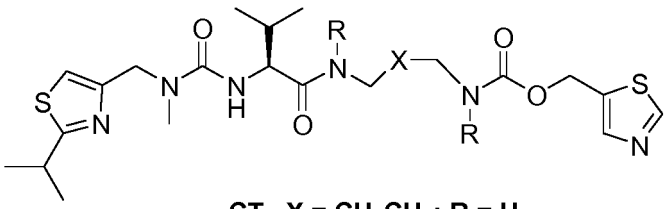
Scheme 78



136 **137**



138



CT X = CH_2CH_2; R = H
CU X = CH_2CH_2; R = Bn
CV X = CH_2; R = Bn

I. PhCHO/$NaBH_4$; II. Cmpd 16/iPr_2NEt; II. Cmpd 13d/EDC/HOBt;

Compound 136

[0451] Compounds **136a-c** are commercially available (Sigma-Aldrich).

Compound 137

[0452] To a solution of Compound **136** (20 mmol) in methanol (25 mL) was added benzaldehyde (40 mmol) dropwise. The mixture was stirred for 2 hours and was cooled to 0 ºC. Sodium borohydride (44 mmol) was added in portions. The mixture was warmed to 25 ºC and stirred for 2 hours. Acetic acid (10 mL) was added and the mixture was stirred for 10 minutes. Methanol was removed and the mixture was partitioned between EtOAc and 3 N NaOH solution. The organic layer was separated and water phase was extracted with EtOAc (2x). The combined organic layers was washed with water, brine, and dried over Na_2SO_4. Concentration gave Compound **137.**

Compound 138

[0453] Compound **138** was prepared following the procedure used to prepare Compound **8,** except that Compound **137** was used instead of Compound **22.**

Example CT

[0454] Example **CT** (70 mg) was prepared following the procedure used to prepare Example **C,** except that Compounds **29** and **138a** was used instead of Compounds **13a** and **8.** .^{1}H-NMR ($CDCl_3$) b 8.79 (1 H, s), 7.86 (1 H, s), 6.97 (1 H, s), 6.49 (1 H, m), 6.15 (1 H, m), 5.28 (2 H, s), 5.20 (1 H, m), 4.44 (2 H, m), 4.05 (1 H, m), 3.25 (5 H, m), 3.0 (3 H, s), 2.24 (1 H, m), 1.8-1.45 (4 H, m), 1.38 (6 H, m), 0.97 (6 H, m); m/z: 525.2 $(M+H)^+$.

Example CU

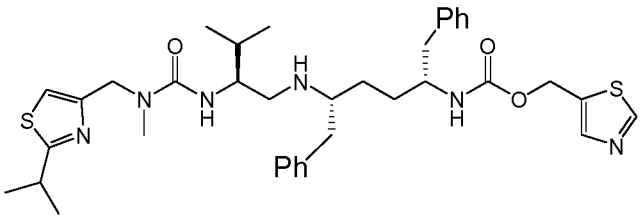
[0455] Example **CU** (140 mg) was prepared following the procedure used to prepare Example **C,** except that Compounds **29** and **138b** was used instead of Compounds **13a** and **8.** ^{1}H-NMR ($CDCl_3$) b 8.78 (1 H, s), 7.85 (1 H, m), 7.4-7.05 (10 H, m), 6.93 (1 H, s), 5.90 (1 H, m), 5.35 (2 H, s), 4.9-4.6 (2 H, m), 4.6-4.4 (4 H, m), 4.2 (1 H, m), 3.4-3.05 (5 H, m), 3.0 (3 H, s), 2.0 (1 H, m), 1.8-1.3 (10 H, m), 0.90 (6 H, m); m/z: 705.2 $(M+H)^+$.

Examle CV

[0456] Example **CV** (145 mg) was prepared following the procedure used to prepare Example **C,** except that Compounds **29** and **138c** was used instead of Compounds **13a** and **8.** ^{1}H-NMR ($CDCl_3$) b 8.76 (1 H, m), 7.86 (1 H, m), 7.4-7.02 (10 H, m), 6.97 (1 H, m), 5.75 (1 H, m), 5.38 (2 H, m), 4.95-4.3 (6 H, m), 4.15 (1 H, m), 3.4-3.0 (5 H, m),, 3.0 (3 H, s), 2.2-1.6 (3 H, m), 1.4 (6 H, m), 0.88 (6 H, m); m/z: 691.2$(M+H)^+$.

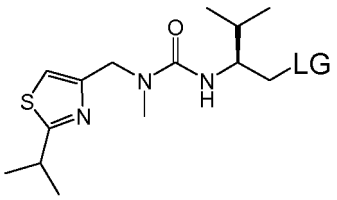
Preparation of Example CW

[0457]



CW

[0458] Example **CW** could be prepared, e.g. by reacting Compound **8** with a compound having the following structure:



where "LG" is a leaving group such as a halogen. Such compounds could be prepared by one-carbon degradation of the corresponding carboxylic acid or ester (e.g., Compounds **28** or **29**) by known methods such as the Hunsdieker reaction or the Kochi reaction or similar methods.

IC_{50} Determinations for Human Liver Cytochrome P450

Materials and General Methods

[0459] Pooled (n ≥ 15 donors) human hepatic microsomal fraction was obtained from BD-Gentest (Woburn, MA) who

also supplied hydroxy-terfenadine, 4'-hydroxydiclofenac and NADPH regenerating system. Ritonavir was prepared from commercial Norvir® oral solution (Abbott Laboratories, Abbott Park, IL). Other reagents were from Sigma-Aldrich (St. Louis, MO) and included terfenadine, fexofenadine, BRL 15572, diclofenac and mefenamic acid.

[0460] Incubations were performed in duplicate in 50 mM potassium phosphate buffer, pH 7.4 with NADPH regenerating system used as described by the manufacturer. The final microsomal protein concentrations had previously been determined to be within the linear range for activity and resulted in less than 20% consumption of substrate over the course of the incubation. The final substrate concentrations used were equal to the apparent Km values for the activities determined under the same conditions. Inhibitors were dissolved in DMSO, and the final concentration of DMSO, from both substrate and inhibitor vehicles, was 1% (v/v). Incubations were performed at 37°C with shaking and were initiated by addition of substrate. Aliquots were then removed at 0, 7 and 15 minutes. Samples were quenched by treatment with an acetonitrile, formic acid, water (94.8%/0.2%/5%, v/v/v) mixture containing internal standard. Precipitated protein was removed by centrifugation at 3000 rpm for 10 min and aliquots of the supernatant were then subjected to LC-MS analysis.

[0461] The LC-MS system consisted of a Waters Acquity UPLC, with a binary solvent manager and a refrigerated (8°C) sample organizer and sample manager, interfaced to a Micromass Quattro Premier tandem mass spectrometer operating in electrospray ionization mode. The column was a Waters Acquity UPLC BEH C_{18} 2.1 x 50 mm, 1.7 μm pore size. Mobile phases consisted of mixtures of acetonitrile, formic acid and water, the composition for mobile phase A being 1%/0.2%/98.8% (v/v/v) and that for mobile phase B being 94.8%/0.2%/5% (v/v/v). The injection volumes were 5 μL and the flow rate was 0.8 mL/min. Concentrations of metabolites were determined by reference to standard curves generated with authentic analytes under the same conditions as the incubations.

[0462] IC_{50} values (the concentration of inhibitor reducing CYP3A activity by 50%) were calculated by non-linear regression using GraphPad Prism 4.0 software and a sigmoidal model.

CYP3A Inhibition Assay

[0463] The potencies of the compounds as inhibitors of human hepatic cytochromes P450 of the CYP3A subfamily (particularly CYP3A4) were assessed using terfenadine oxidase, a well-characterized CYP3A-selective activity described in Ling, K.-H.J., et al Drug Metab. Dispos. 23, 631-636, (1995) and Jurima-Romet, et al Drug Metab. Dispos. 22, 849-857, (1994). The final concentrations of microsomal protein and terfenadine substrate were 0.25 mg/mL and 3 μM, respectively. Metabolic reactions were terminated by treatment with seven volumes of quench solution containing 0.1 μM BRL 15572 as internal standard. A further 8 volumes of water were added before centrifugation and aliquots of the supernatant were removed for analysis.

[0464] For LC-MS analysis chromatographic elution was achieved by a series of linear gradients starting at 20% B and holding for 0.1 minutes, then increasing to 80% B over 1.5 minutes, holding for 0.4 minutes and then returning to the starting conditions for 0.05 min. The system was allowed to re-equilibrate for at least 0.25 minutes prior to the next injection. The mass spectrometer was operated in positive ion mode and the following precursor ($[M+H]^+$)/product ion pairs were monitored and quantified using MassLynx 4.0 (SP4, 525) software: hydroxy-terfenadine 488.7/452.4, fexofenadine 502.7/466.4 and BRL 15572 407.5/209.1. Terfenadine oxidase activity was determined from the sum of hydroxy-terfenadine and carboxy-terfenadine (fexofenadine) metabolites.

CYP2C9 Inhibition Assay

[0465] The potencies of the compounds as inhibitors of human hepatic CYP2C9 were assessed using diclofenac 4'-hydroxylase, an activity specific for this enzyme, as described in Leeman, T., et al Life Sci. 52, 29-34, (1992). The final concentrations of microsomal protein and diclofenac substrate were 0.08 mg/mL and 4 μM, respectively. Metabolic reactions were terminated by treatment with three volumes of quench solution containing 1 μM mefenamic acid as internal standard. After centrifugation a further 4 volumes of water were added. Aliquots of the supernatant were then subjected to LC-MS analysis.

[0466] For LC-MS analysis chromatographic elution was achieved by a series of linear gradients starting at 20% B and holding for 0.3 minutes, then increasing to 99% B over 1.2 minutes, holding for 0.5 minutes and then returning to the starting conditions for 0.25 min. The system was allowed to re-equilibrate for at least 0.25 minutes prior to the next injection. The mass spectrometer was operated in negative ion mode and the following precursor ($[M-H]^-$)/product ion pairs were monitored and quantified: 4'-hydroxy-diclofenac 312.4/294.2 and mefenamic acid 242.4/224.2.

Biological Assays Used for the Characterization of HIV Protease Inhibitors

HIV-1 Protease Enzyme Assay (*Ki*)

[0467] The assay is based on the fluorimetric detection of synthetic hexapeptide substrate cleavage by HIV-1 protease

in a defined reaction buffer as initially described by M.V. Toth and G.R.Marshall, Int. T. Peptide Protein Res. 36, 544 (1990) (herein incorporated by reference in its entirety for all purposes).

[0468] The assay employed (2-aminobenzoyl)Thr-Ile-Nle-(p-nitro)Phe-Gln-Arg as the substrate and recombinant HIV-1 protease expressed in E.Coli as the enzyme. Both of the reagents were supplied by Bachem California, Inc. (Torrance, CA; Cat. no. H-2992). The buffer for this reaction was 100 mM ammonium acetate, pH 5.3, 1 M sodium chloride, 1 mM ethylendiaminetetraacetic acid, 1 mM dithiothreitol, and 10% dimethylsulfoxide.

[0469] To determine the inhibition constant K_i, a series of solutions were prepared containing identical amount of the enzyme (1 to 2.5 nM) and the inhibitor to be tested at different concentrations in the reaction buffer. The solutions were subsequently transferred into a white 96-well plate (190 μl each) and preincubated for 15 min at 37 °C The substrate was solublized in 100% dimethylsulfoxide at a concentration of 800 μM and 10 μl of 800 μM substrate was added into each well to reach a final substrate concentration of 40 μM. The real-time reaction kinetics was measured at 37 °C using a Gemini 96-well plate fluorimeter (Molecular Devices, Sunnyvale, CA) at λ(Ex) = 330 nm and λ(Em) 420 nm. Initial velocities of the reactions with different inhibitor concentrations were determined and the K_i value (in picomolar concentration units) was calculated by using EnzFitter program (Biosoft, Cambridge, U.K.) according to an algorithm for tight-binding competitive inhibition described by Ermolieff J., Lin X., and Tang J., Biochemistry 36, 12364 (1997).

HIV-1 Protease Enzyme Assay (IC_{50})

[0470] As for the K_i assay, above, the IC_{50} assay is based on the fluorimetric detection of synthetic hexapeptide substrate cleavage by HIV-1 protease in a defined reaction buffer as initially described by M.V. Toth and G.R.Marshall, Int. T. Peptide Protein Res. 36, 544 (1990).

[0471] The assay employed (2-aminobenzoyl)Thr-Ile-Nle-(p-nitro)Phe-Gln-Arg as the substrate and recombinant HIV-1 protease expressed in E.Coli as the enzyme. Both of the reagents were supplied by Bachem California, Inc. (Torrance, CA; Cat. nos. H-2992 and H-9040, respectively). The buffer for this reaction was 100 mM ammonium acetate, pH 5.5, 1 M sodium chloride, 1 mM ethylendiaminetetraacetic acid, and 1 mM dithiothreitol, and 10% dimethylsulfoxide.

[0472] To determine the IC50 value, 170 μL of reaction buffer was transferred into the wells of a white 96-well microtiter plate. A series of 3-fold dilutions in DMSO of the inhibitor to be tested was prepared, and 10 μL of the resulting dilutions was transferred into the wells of the microtiter plate. 10 μL of a 20-50 nM enzyme stock solution in reaction buffer was added to each well of the 96-well plate to provide a final enzyme concentration of 1-2.5 nM. The plates were then preincubated for 10 minutes at 37ºC. The substrate was solublized in 100% dimethylsulfoxide at a concentration of 400 μM and 10 μl of the 400 μM substrate was added into each well to reach a final substrate concentration of 20 μM. The real-time reaction kinetics were measured using a Gemini 96-well plate fluorimeter (Molecular Devices, Sunnyvale, CA) at A(Ex) = 330 nm and λ(Em) = 420 nm. Initial velocities of the reactions with different inhibitor concentrations were determined and the IC_{50} value (in nanomolar concentration units) was calculated by using GraphPad Prism™ software to fit nonlinear regression curves.

Anti-HIV-1 Cell Culture Assay (EC50)

[0473] The assay is based on quantification of the HIV-1-associated cytopathic effect by a colorimetric detection of the viability of virus-infected cells in the presence or absence of tested inhibitors. HIV-1-induced cell death was determined using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) which is converted only by intact cells into a product with specific absorption characteristics as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR, J. Natl. Cancer Inst. 81, 577 (1989) (herein incorporated by reference in its entirety for all purposes).

[0474] MT2 cells (NIH AIDS reagent program, Cat # 237) maintained in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics were infected with the wild-type HIV-1 strain IIIB (Advanced Biotechnologies, Columbia, MD) for 3 hours at 37 °C using the virus inoculum corresponding to a multiplicity of infection equal to 0.01. The infected cells in culture media were distributed into a 96-well plate (20,000 cells in 100 μl/well), and incubated in the presence of a set of solutions containing 5-fold serial dilutions of the tested inhibitor (100 μl/well) for 5 days at 37 °C. Samples with untreated infected and untreated mock-infected control cells were also distributed to the 96-well plate and incubated under the same conditions.

[0475] To determine the antiviral activity of the tested inhibitors, a substrate XTT solution (6 mL per assay plate) at a concentration of 2 mg/mL in a phosphate-buffered saline pH 7.4 was heated in water-bath for 5 min at 55 °C before 50 μl of N-methylphenazonium methasulfate (5 μg/mL) was added per 6 mL of XTT solution. After removing 100 μl media from each well on the assay plate, 100 μl of the XTT substrate solution was added to each well. The cells and the XTT solution were incubated at 37 °C for 45 to 60 min in a CO_2 incubator. To inactivate the virus, 20 μl of 2% Triton X-100 was added to each well. Viability, as determined by the amount of XTT metabolites produced, was quantified spectrophotometrically by the absorbance at 450 nm (with subtraction of the background absorbance at 650 nm). Data from

the assay was expressed as the percentage absorbance relative to untreated control and the fifty percent effective concentration (EC_{50}) was calculated as the concentration of compound that effected an increase in the percentage of XTT metabolite production in infected, compound treated cells to 50% of that produced by uninfected, compound-free cells.

Anti-HIV-1 Cell Culture Assay (EC_{50}) in presence of 40% Human Serum or Human Serum Proteins

[0476] This assay is almost identical to the Anti-HIV-1 Cell Culture Assay described above, except that the infection was made in the presence or absence of 40% human serum (Type AB Male Cambrex 14-498E) or human serum proteins (Human α-acid Glycoprotein, Sigma G-9885; Human Serum Albumin, Sigma A1653, 96-99%) at physiological concentration. The HIV-1-induced cell death was determined as described above, except that the infected cells distributed in the 96-well plate were incubated in 80% Human Serum (2X concentration) or in 2 mg/mL Human α-acid Glycoprotein + 70 mg/mL HSA (2X concentration) rather than in culture media.

Cytotoxicity Cell Culture Assay (CC_{50})

[0477] The assay is based on the evaluation of cytotoxic effect of tested compounds using a metabolic substrate 2,3-bis(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT) as described by Weislow OS, Kiser R, Fine DL, Bader J, Shoemaker RH and Boyd MR, J. Natl. Cancer Inst. 81, 577 (1989). This assay is almost identical to the previous assay described (Anti-HIV-1 Cell Culture Assay), except that the cells were not infected. The compound induced cell death (or growth reduction) was determined as previously described.

[0478] MT-2 cells maintained in RPMI-1640 medium supplemented with 5% fetal bovine serum and antibiotics were distributed into a 96-well plate (20,000 cells in 100 μl/well) and incubated in the presence or absence of 5-fold serial dilutions of the tested inhibitor (100 μl/well) for 5 days at 37 °C. Controls included untreated infected cells and infected cells protected by 1 μM of P4405 (Podophyllotoxin, Sigma Cat # P4405).

[0479] To determine cytotoxicity, an XTT solution (6 mL per assay plate) at a concentration of 2 mg/mL in phosphate-buffered saline pH 7.4 was heated in the dark in a water-bath for 5 min at 55 °C before 50 μl of N-methylphenazonium methasulfate (5 μg/mL) was added per 6 mL of XTT solution. After removing 100 μL media from each well on the assay plate, 100 μL of the XTT substrate solution was added to each well. The cells and the XTT solution were incubated at 37 °C for 45 to 60 min in a CO_2 incubator. To inactivate the virus, 20 μl of 2% Triton X-100 was added to each well. Viability, as determined by the amount of XTT metabolites produced, is quantified spectrophotometrically by the absorbance at 450 nm (with subtraction of the background absorbance at 650 nm). Data from the assay is expressed as the percentage absorbance relative to untreated control, and the fifty percent cytotoxicity concentration (EC_{50}) was calculated as the concentration of compound that effected an increase in the percentage of cell growth in compound treated cells to 50% of the cell growth provided by uninfected, compound-free cells.

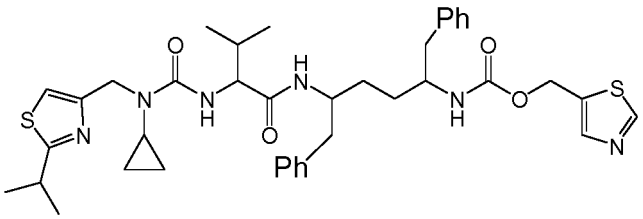
[0480] Experimental data based on representative Examples **A-CV** demonstrate that the compounds of Formula (I) of the present invention can have a CYP450 3A4 inhibition activity in a range represented by an IC_{50} from about 100 nM to about 4700 nM, and a CYP450 2C9 inhibition activity in a range represented by an IC_{50} from about 100 nM to about 4200 nM.

[0481] Experimental data based on representative Examples **A-CV** demonstrate that the compounds of Formula (I) of the present invention can have a protease inhibition activity in a range represented by HIV EC_{50} from about 140 nM to greater than about 1000 nM.

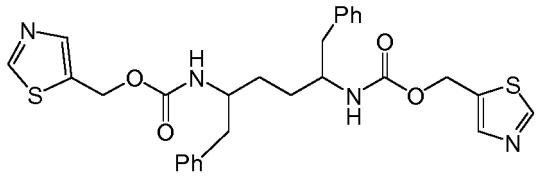
[0482] Experimental data based on representative Examples **P, S,** and **T** have a CYP450 3A4 inhibition activity in a range represented by an IC_{50} from about 80-150 nM, a CYP450 2C9 inhibition activity in a range represented by an IC_{50} from about 1000-10,000 nM, and a protease inhibition activity in a range represented by HIV EC_{50} greater than about 20,000 nM.

Claims

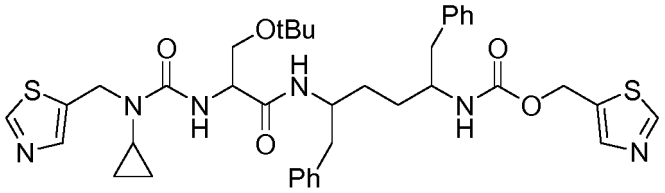
1. A compound of the formula



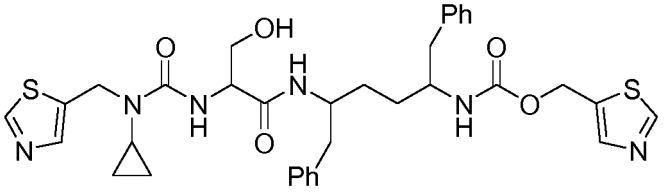
,



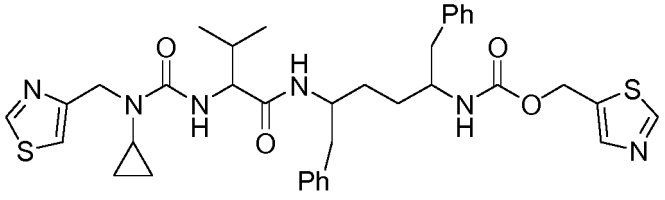
,



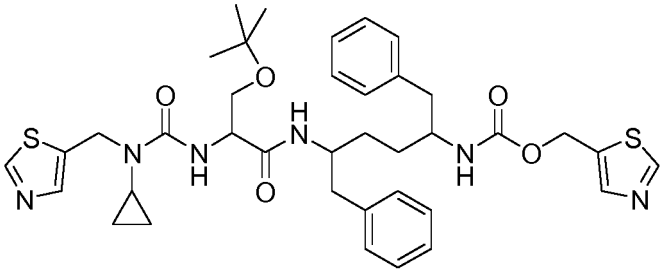
,



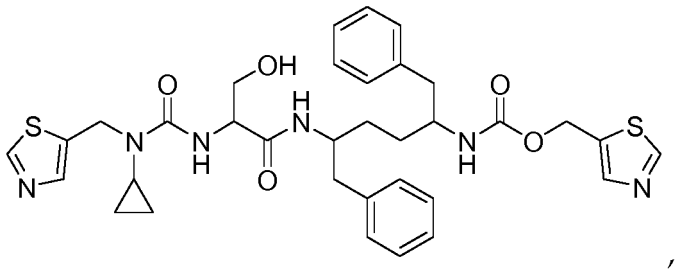
,



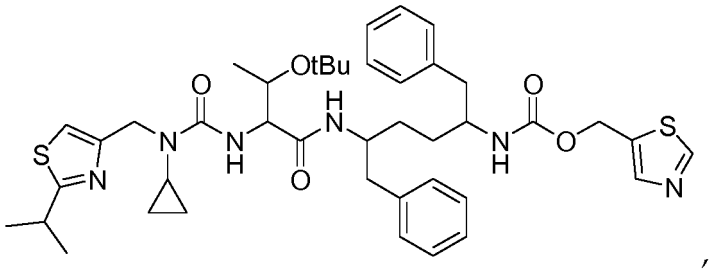
,



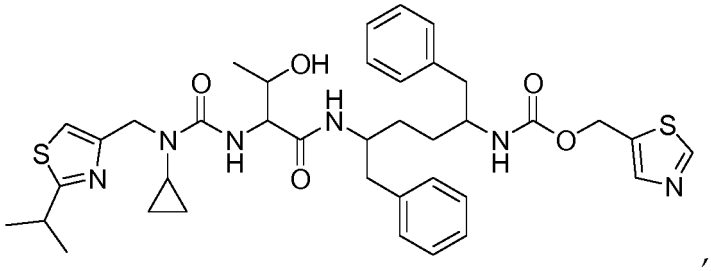
,



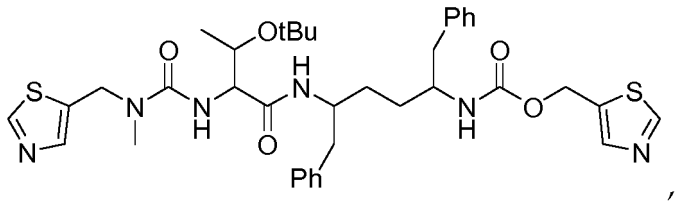
,



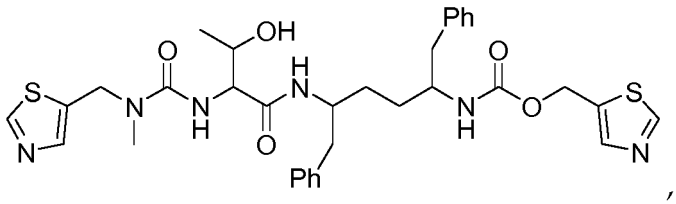
,



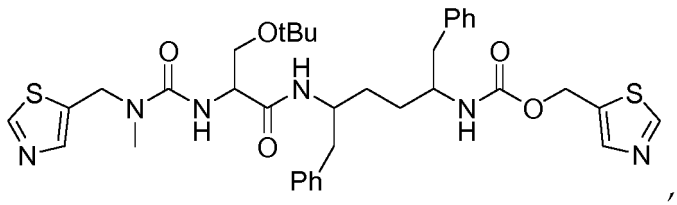
,



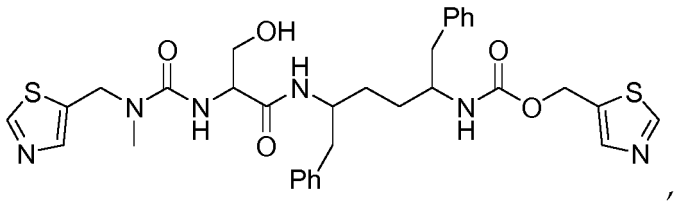
,



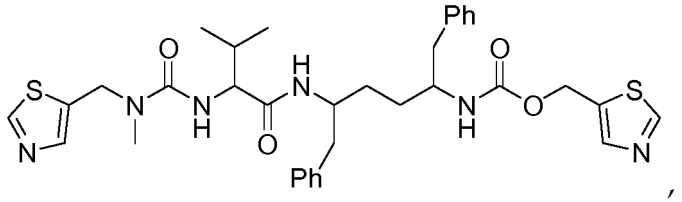
,



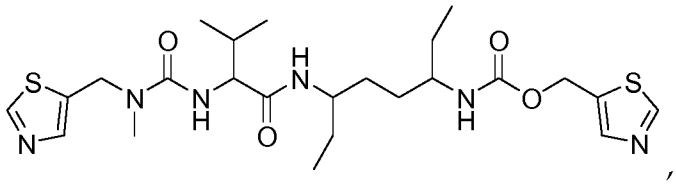
,



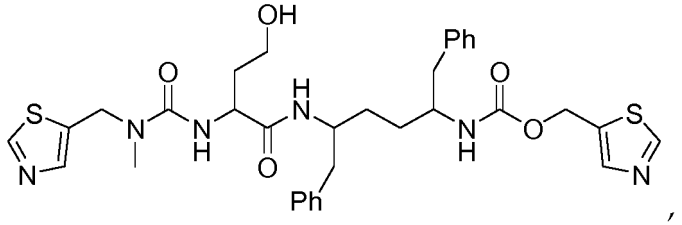
,



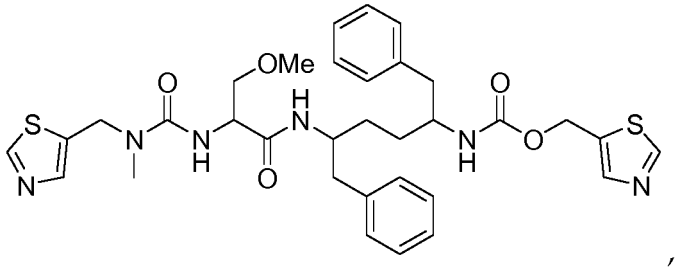
,



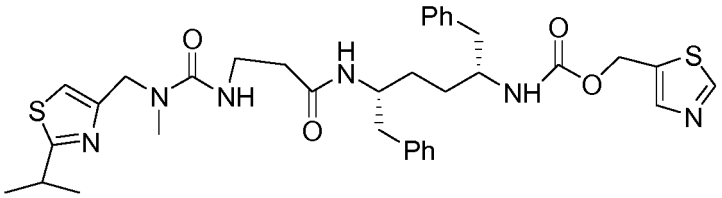
,



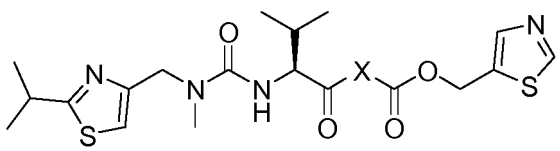
,



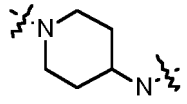
,



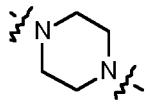
,

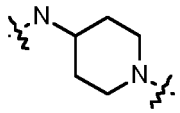


X = $NH(CH_2)_2NH$
X = $NH(CH_2)_3NH$

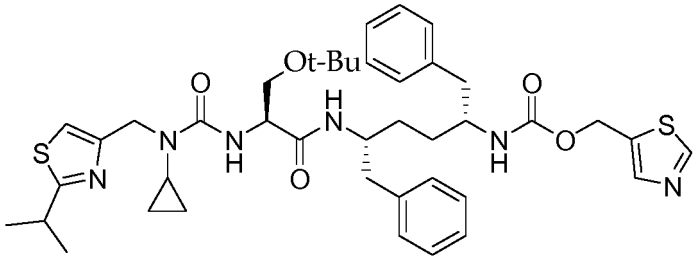


X =

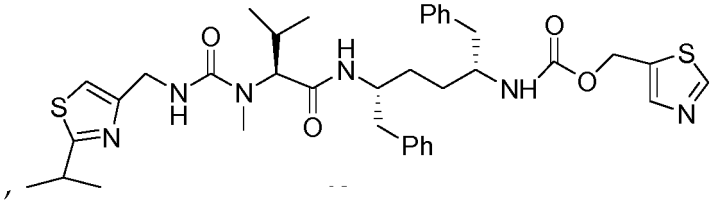




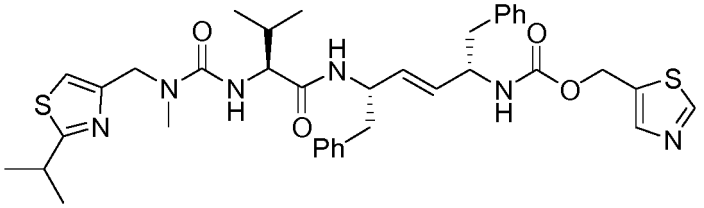
,



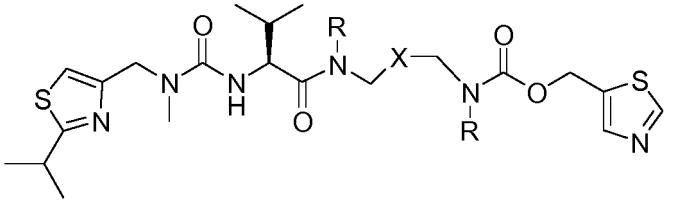
,



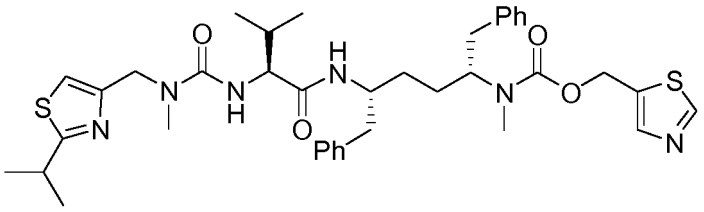
, ,



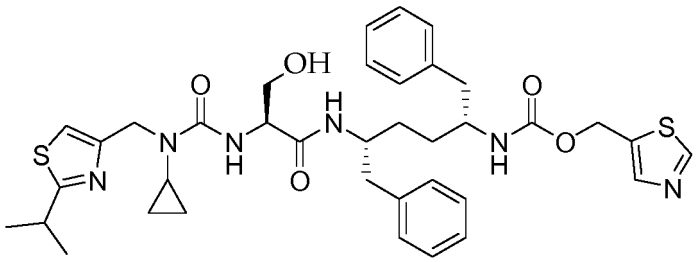
,



X = CH_2, R = Bn,

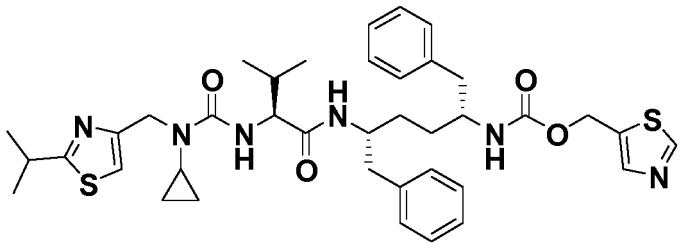


,

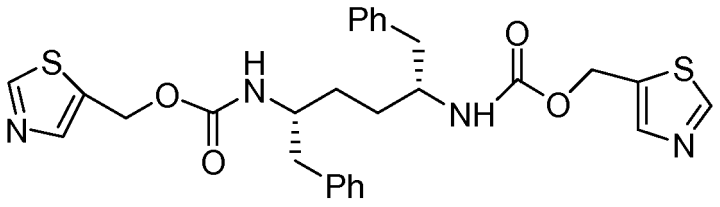


or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

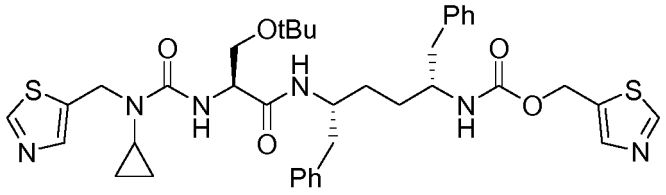
2. A compound of claim 1 of the formula



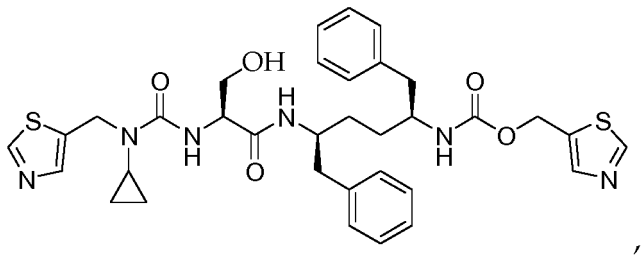
,



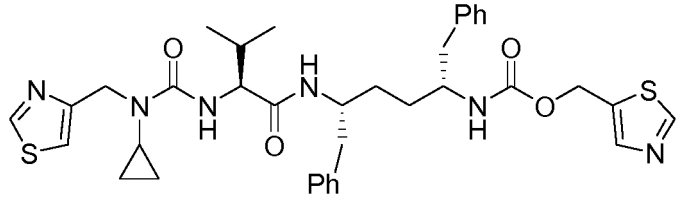
,



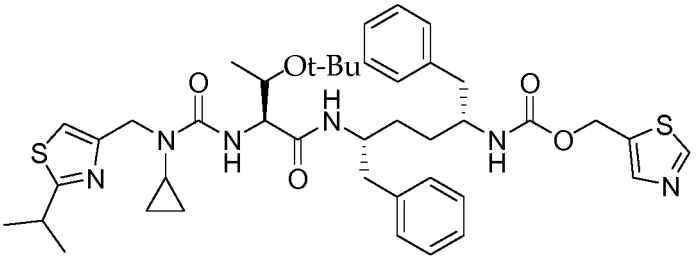
,



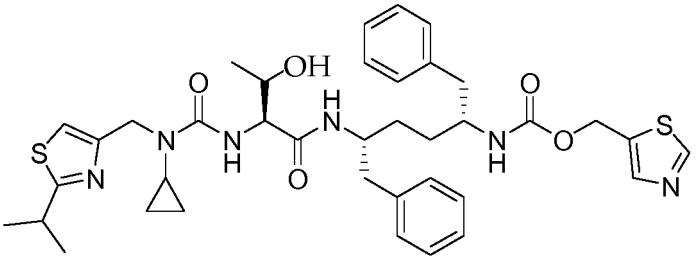
,



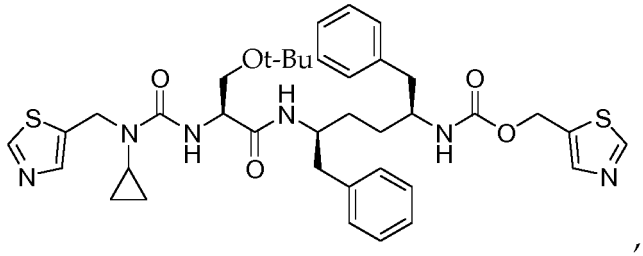
,



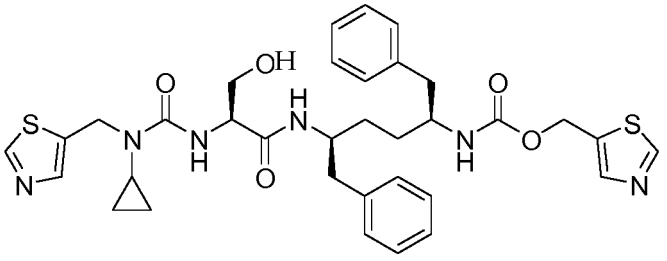
,



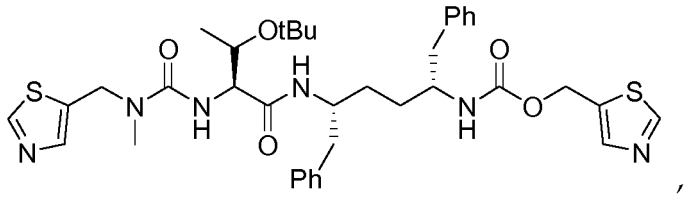
,



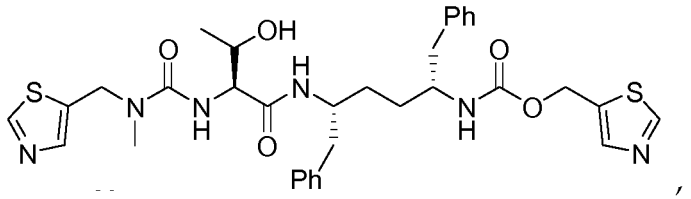
,



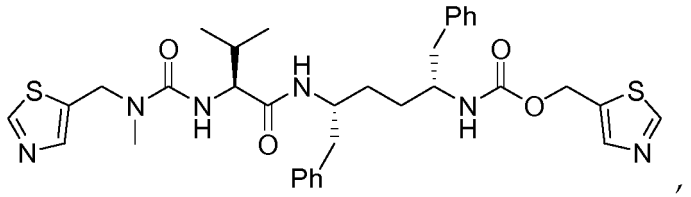
,



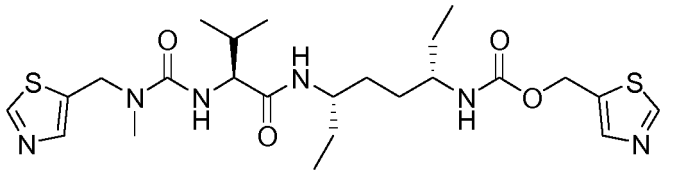
,



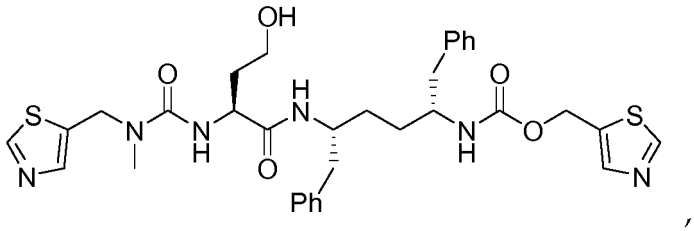
,



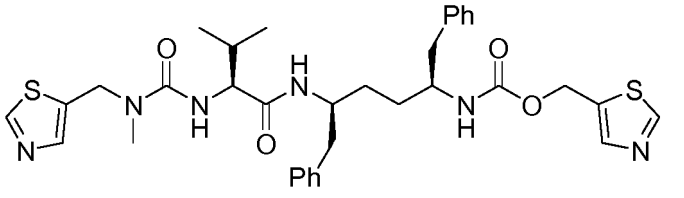
,



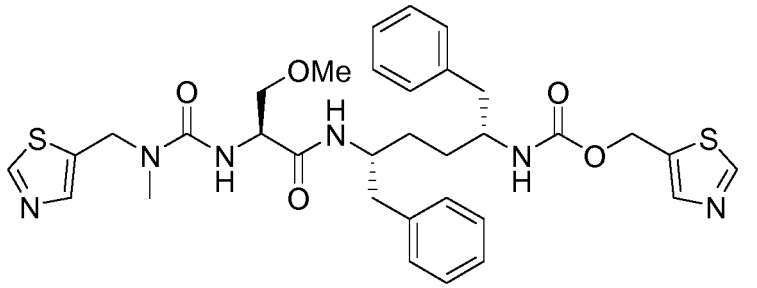
,



,



,



or a pharmaceutically acceptable salt, solvate, and/or ester thereof.

3. A pharmaceutical composition comprising a compound of claim 1 or 2, or a pharmaceutically acceptable salt, solvate, and/or ester thereof, and a pharmaceutically acceptable carrier or excipient.

4. The pharmaceutical composition of claim 3, further comprising at least one additional therapeutic agent which is metabolized by cytochrome P450 monooxygenase, one or more isozymes of P450, in particular cytochrome P450 monooxygenase 3A4.

5. The pharmaceutical composition of claim 4, wherein the at least one additional therapeutic agent is selected from the group consisting of HIV protease inhibiting compounds, HIV non-nucleoside inhibitors of reverse transcriptase, HIV nucleoside inhibitors of reverse transcriptase, HIV nucleotide inhibitors of reverse transcriptase, HIV integrase inhibitors, gp41 inhibitors, CXCR4 inhibitors, gp120 inhibitors, CCR5 inhibitors, capsid polymerization inhibitors, interferons, ribavirin analogs, NS3 protease inhibitors, alpha-glucosidase 1 inhibitors, hepatoprotectants, non-nucleoside inhibitors of HCV, other drugs for treating HCV, and combinations thereof.

6. The pharmaceutical composition of claim 5, wherein:

(1) said HIV protease inhibitors are selected from the group consisting of amprenavir, atazanavir, fosamprenavir, indinavir, lopinavir, ritonavir, nelfinavir, saquinavir, tipranavir, brecanavir, darunavir, TMC-126, TMC-114, mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35, and AG 1859;
(2) said HIV non-nucleoside inhibitors of reverse transcriptase are selected from the group consisting of capravirine, emivirine, delaviridine, efavirenz, nevirapine, (+) calanolide A, etravirine, GW5634, DPC-083, DPC-961, DPC-963, MIV-150, and TMC-120, TMC-278 (rilpivirene), BILR 355 BS, VRX 840773, UK-453061, and RDEA806;
(3) said HIV nucleoside inhibitors of reverse transcriptase are selected from the group consisting of zidovudine, emtricitabine, didanosine, stavudine, zalcitabine, lamivudine, abacavir, amdoxovir, elvucitabine, alovudine, MIV-210, racivir (±-FTC), D-d4FC, phosphazide, fozivudine tidoxil, apricitibine (AVX754), amdoxovir, KP-1461, and fosalvudine tidoxil (formerly HDP 99.0003),;
(4) said HIV nucleotide inhibitors of reverse transcriptase are selected from the group consisting of tenofovir and adefovir;
(5) said HIV integrase inhibitors are selected from the group consisting of curcumin, derivatives of curcumin, derivatives of curcumin, chicoric acid, derivatives of chicoric acid, 3,5-dicaffeoylquinic acid, derivatives of 3,5-dicaffeoylquinic acid, aurintricarboxylic acid, derivatives of aurintricarboxylic acid, caffeic acid phenethyl ester, derivatives of caffeic acid phenethyl ester, tyrphostin, derivatives of tyrphostin, quercetin, derivatives of quercetin, S-1360, zintevir (AR-177), L-870812, L-870810, MK-0518 (raltegravir), elvitegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048, and BA 011;
(6) said gp41 inhibitor are selected from the group consisting of enfuvirtide, sifuvirtide, FB006M, and TRI-1144;
(7) said CXCR4 inhibitor is AMD-070;
(8) said entry inhibitor is SP01A;
(9) said gp120 inhibitor is BMS-488043 or BlockAide/ CR;
(10) said G6PD and NADH-oxidase inhibitor is immunitin;
(11) said CCR5 inhibitors are selected from the group consisting of aplaviroc, vicriviroc, maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer), and CCR5mAb004;
(12) said other drugs for treating HIV are selected from the group consisting of BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bevirimat), Ampligen, HRG214, Cytolin, VGX-410,

KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889, and PA-1050040 (PA-040);
(13) said interferons are selected from the group consisting of pegylated rIFN-alpha 2b, pegylated rIFN-alpha 2a, rIFN-alpha 2b, rIFN-alpha 2a, consensus IFN alpha (infergen), feron, reaferon, intermax alpha, r-IFN-beta, infergen + actimmune, IFN-omega with DUROS, albuferon, locteron, Albuferon, Rebif, Oral interferon alpha, IFNalpha-2b XL, AVI-005, PEG-Infergen, and Pegylated IFN-beta;
(14) said ribavirin analogs are selected from the group consisting of rebetol, copegus, and viramidine (taribavirin);
(15) said NS5b polymerase inhibitors are selected from the group consisting of NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554, and GSK625433;
(16) said NS3 protease inhibitor are selected from the group consisting of SCH-503034 (SCH-7), VX-950 (telaprevir), BILN-2065, BMS-605339, and ITMN-191;
(17) said alpha-glucosidase 1 inhibitors are selected from the group consisting of MX-3253 (celgosivir) and UT-231B;
(18) said hepatoprotectants are selected from the group consisting of IDN-6556, ME 3738, LB-84451, and MitoQ;
(19) said non-nucleoside inhibitors of HCV are selected from the group consisting of benzimidazole derivatives, benzo-1,2,4-thiadiazine derivatives, phenylalanine derivatives, A-831, and A-689; and
(20) said other drugs for treating HCV are selected from the group consisting of zadaxin, nitazoxanide (alinea), BIVN-401 (virostat), PYN-17 (altirex), KPE02003002, actilon (CPG-10101), KRN-7000, civacir, GI-5005, ANA-975, XTL-6865, ANA 971, NOV-205, tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanide, and VX-497 (merimepodib).

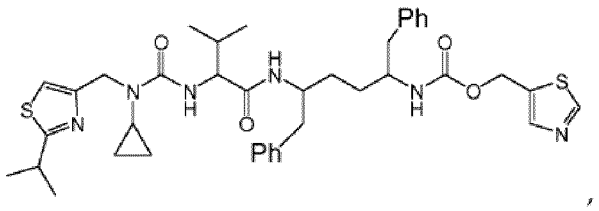
7. A compound of claim 1 or 2 for use in therapy.

8. A compound of claim 1 or 2 for use in improving the pharmacokinetics of a drug which is metabolized by cytochrome P450 monooxygenase, increasing the blood plasma level of a drug which is metabolized by cytochrome P450 monooxygenase, inhibiting cytochrome P450 monooxygenase, treating an HIV infection, or treating an HCV infection in a patient.

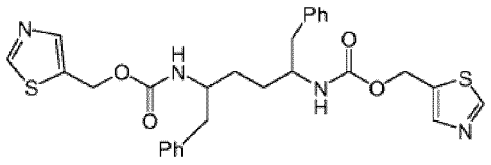
9. A compound for use according to claim 8, wherein the cytochrome P450 monooxygenase is cytochrome P450 monooxygenase 3A.

Patentansprüche

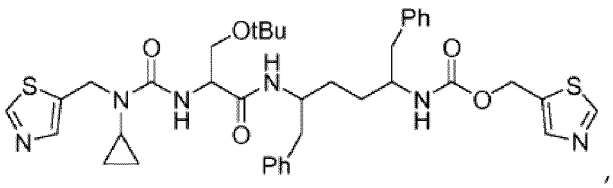
1. Verbindung der Formel:



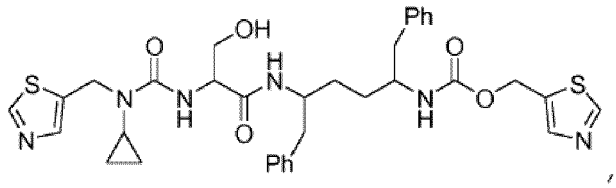
,



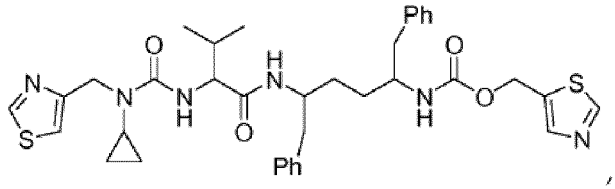
,



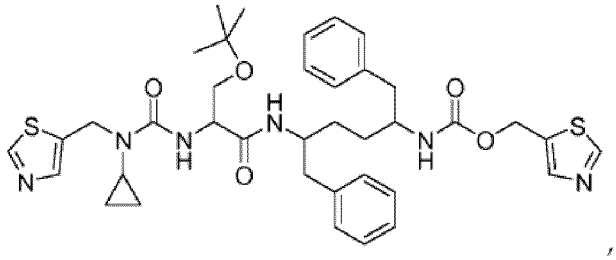
,



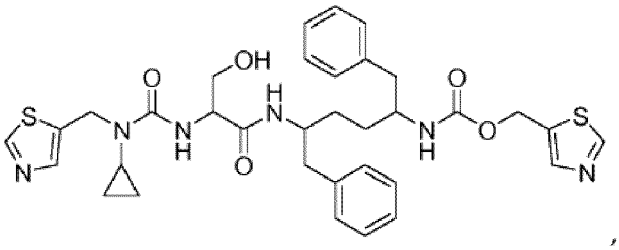
,



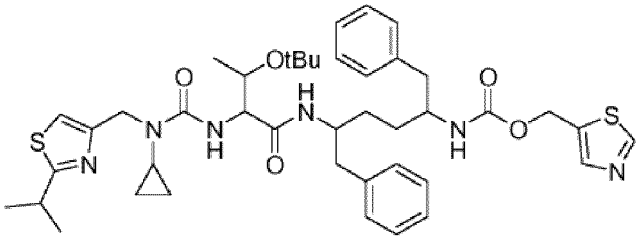
,



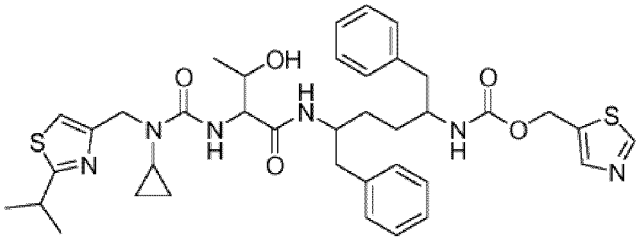
,



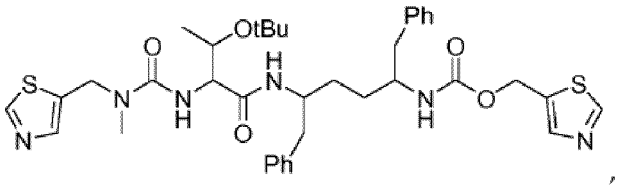
,

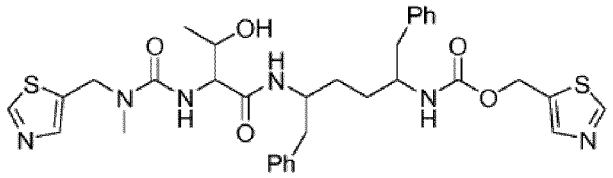


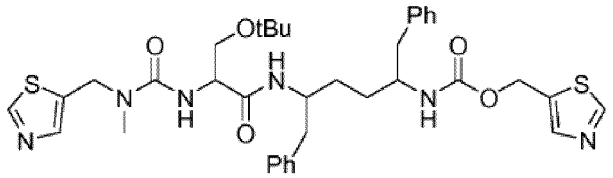
,

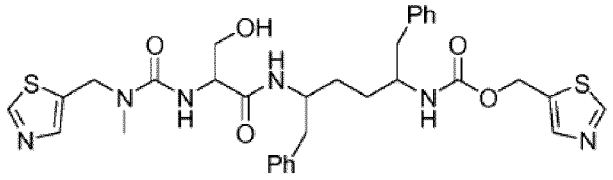


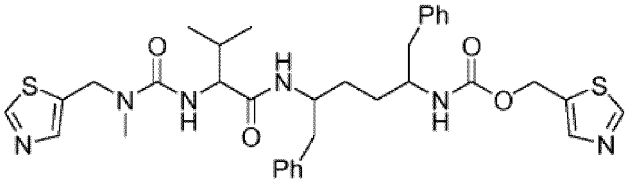
,

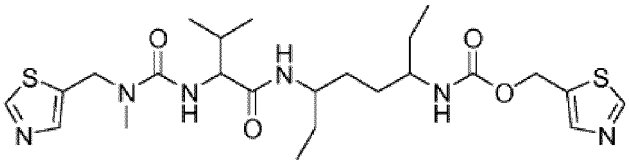


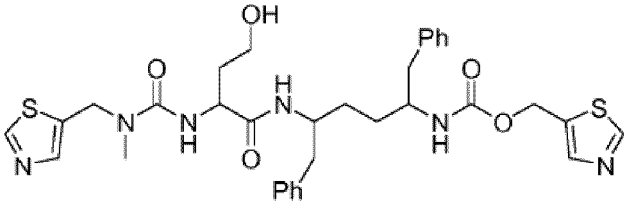


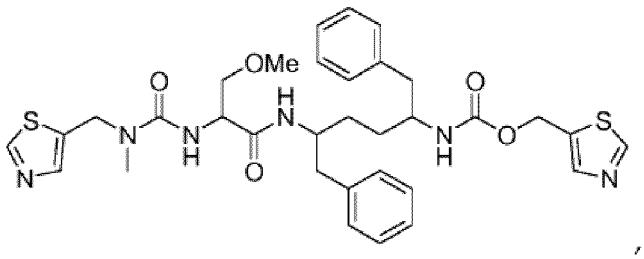


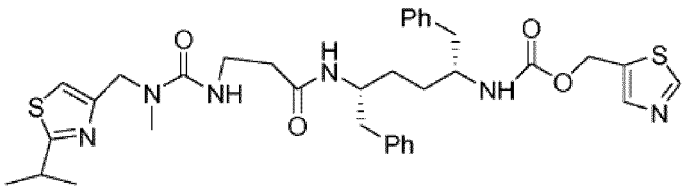


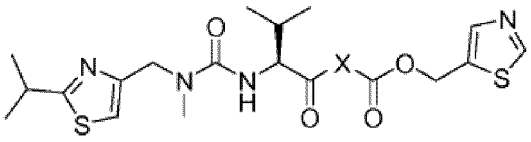






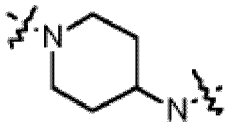




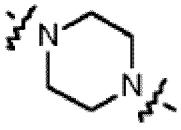


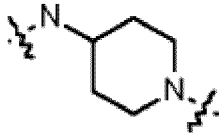
X = $NH(CH_2)_2NH$

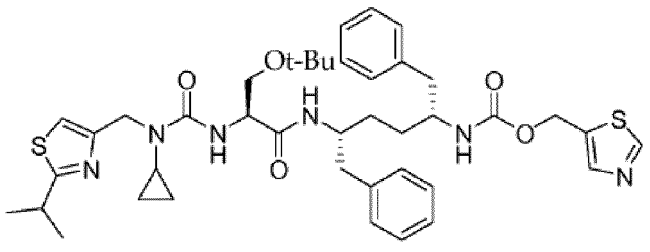
X = $NH(CH_2)_3NH$

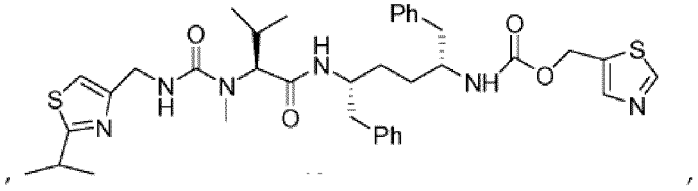


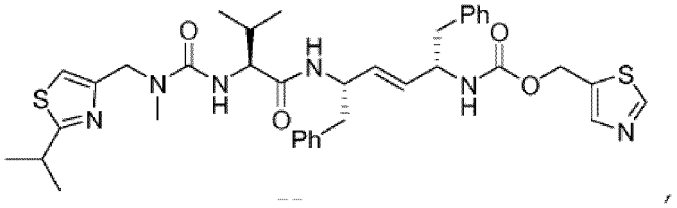
X =

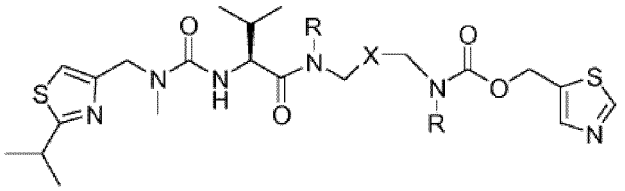




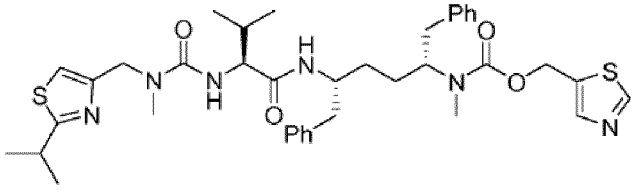


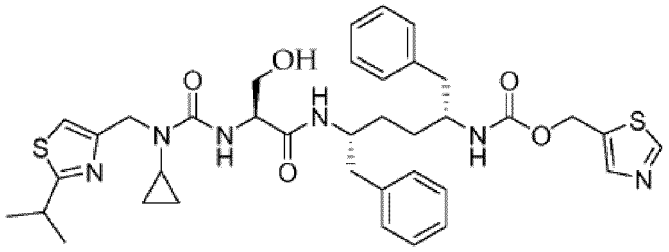






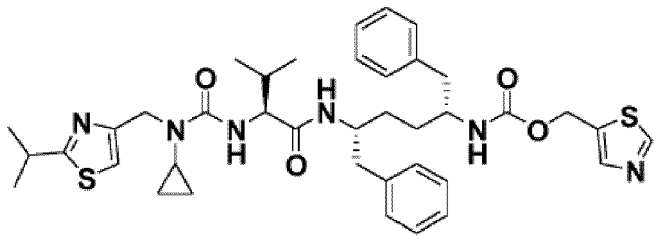
X = CH_2, R = Bn

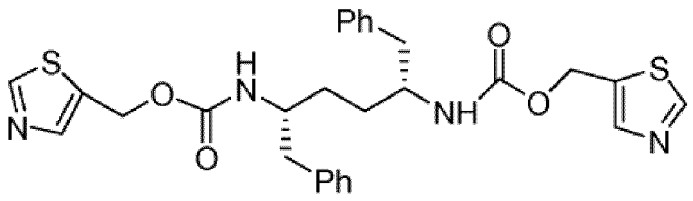


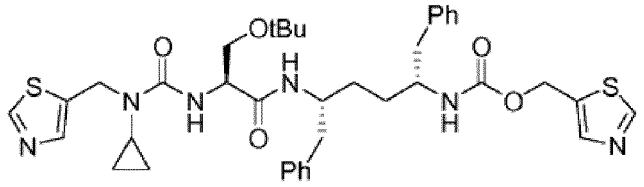


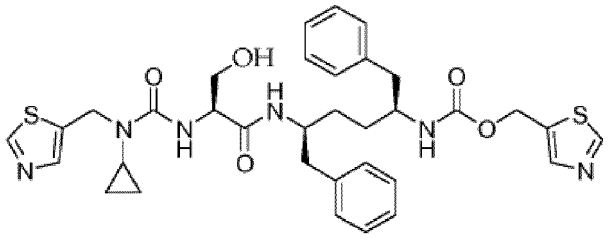
oder ein pharmazeutisch unbedenkliches Salz, ein pharmazeutisch unbedenkliches Solvat und/oder ein pharmazeutisch unbedenklicher Ester davon.

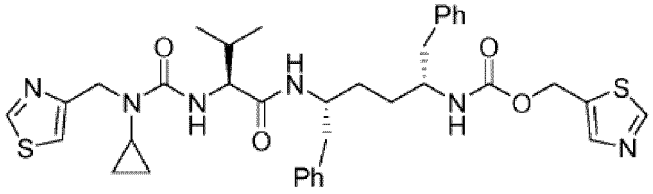
2. Verbindung nach Anspruch 1 mit der Formel:

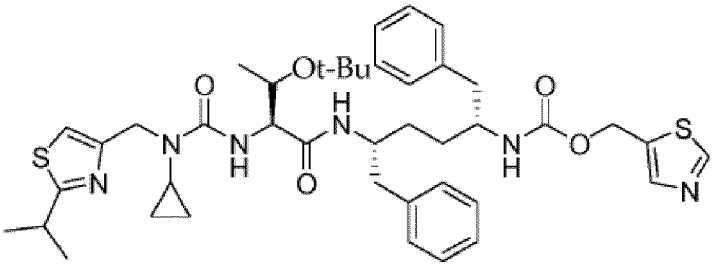


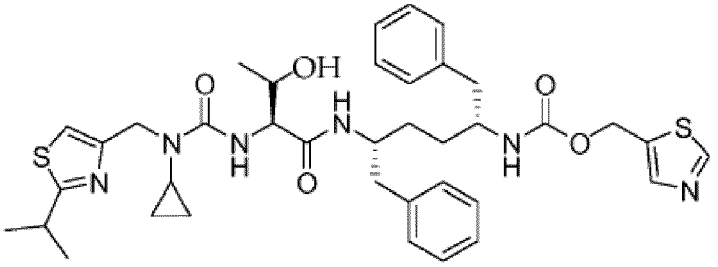


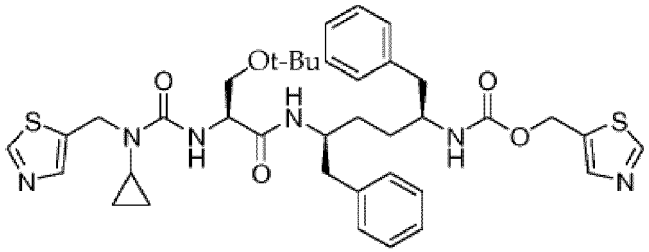


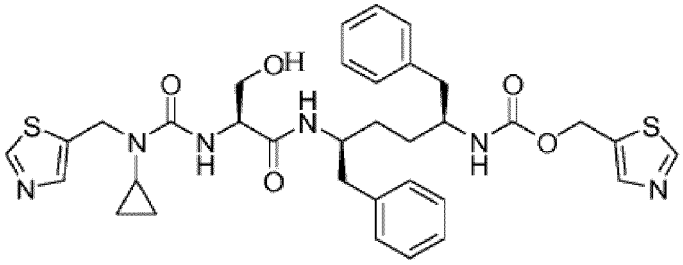


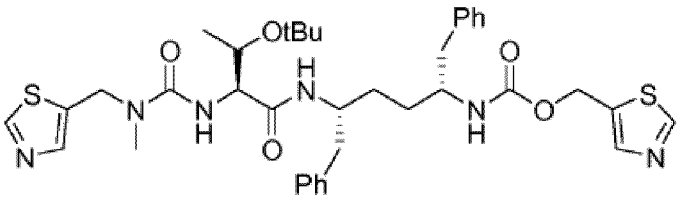


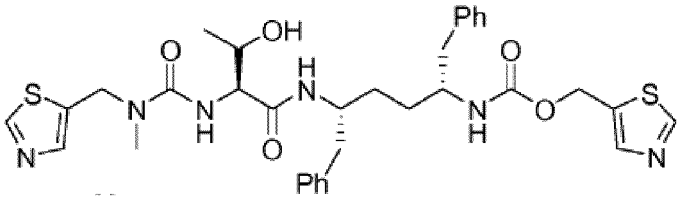


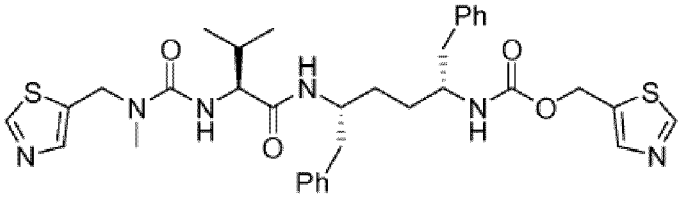


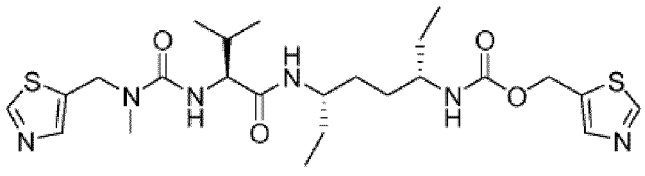

Ot-Bu

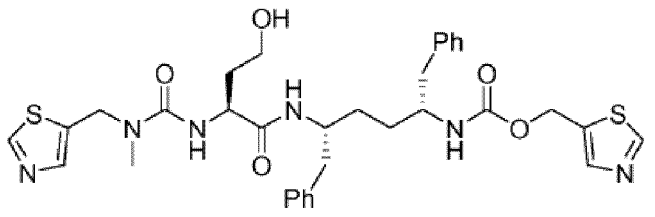

OH

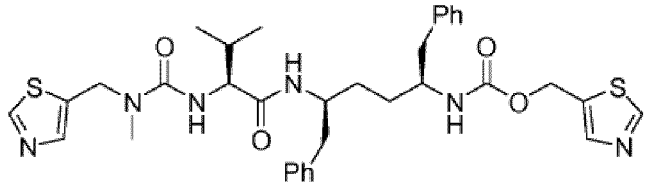

OtBu
Ph
Ph

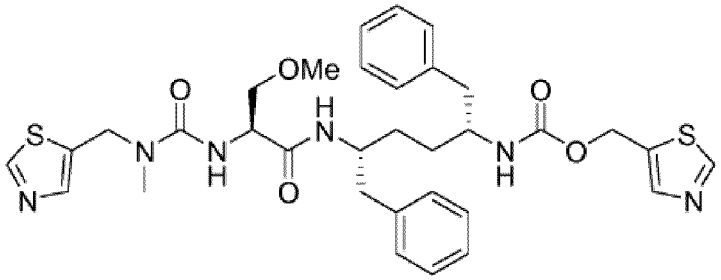

OH
Ph
Ph


Ph
Ph









oder ein pharmazeutisch unbedenkliches Salz, ein pharmazeutisch unbedenkliches Solvat und/oder ein pharmazeutisch unbedenklicher Ester davon.

3. Pharmazeutische Zusammensetzung, umfassend eine Verbindung nach Anspruch 1 oder 2 oder ein pharmazeutisch unbedenkliches Salz, ein pharmazeutisch unbedenkliches Solvat und/oder einen pharmazeutisch unbedenklichen Ester davon und einen pharmazeutisch unbedenklichen Träger oder Exzipienten.

4. Pharmazeutische Zusammensetzung nach Anspruch 3, weiterhin umfassend mindestens ein zusätzliches Therapeutikum, welches durch Cytochrom-P450-Monooxygenase, ein oder mehrere Isozyme von P450, insbesondere Cytochrom-P450-Monooxygenase 3A4, metabolisiert wird.

5. Pharmazeutische Zusammensetzung nach Anspruch 4, wobei das mindestens eine zusätzliche Therapeutikum ausgewählt ist aus der Gruppe bestehend aus HIV-Protease-inhibierenden Verbindungen, HIV-Nichtnukleosid-Inhibitoren von reverser Transkriptase, HIV-Nukleosid-Inhibitoren von reverser Transkriptase, HIV-Nukleotid-Inhibitoren von reverser Transkriptase, HIV-Integrase-Inhibitoren, gp41-Inhibitoren, CXCR4-Inhibitoren, gp120-Inhibitoren, CCR5-Inhibitoren, Capsidpolymerisationsinhibitoren, Interferonen, Ribavirinanaloga, NS3-Protease-Inhibitoren, α-Glucosidase-1-Inhibitoren, leberschützenden Mitteln, Nichtnukleosid-Inhibitoren von HCV, anderen Arzneimitteln zur Behandlung von HCV und Kombinationen davon.

6. Pharmazeutische Zusammensetzung nach Anspruch 5, wobei:

1) die HIV-Protease-Inhibitoren ausgewählt sind aus der Gruppe bestehend aus Amprenavir, Atazanavir, Fosamprenavir, Indinavir, Lopinavir, Ritonavir, Nelfinavir, Saquinavir, Tipranavir, Brecanavir, Darunavir, TMC-126, TMC-114, Mozenavir (DMP-450), JE-2147 (AG1776), L-756423, RO0334649, KNI-272, DPC-681, DPC-684, GW640385X, DG17, PPL-100, DG35 und AG 1859,
2) die HIV-Nichtnukleosid-Inhibitoren von reverser Transkriptase ausgewählt sind aus der Gruppe bestehend aus Capravirin, Emivirin, Delaviridin, Efavirenz, Nevirapin, (+)-Calanolid A, Etravirin, GW5634, DPC-083, DPC-961, DPC-963, MIV-150 und TMC-120, TMC-278 (Rilpiviren), BILR 355 BS, VRX 840773, UK-453061 und RDEA806,
3) die HIV-Nukleosid-Inhibitoren von reverser Transkriptase ausgewählt sind aus der Gruppe bestehend aus

Zidovudin, Emtricitabin, Didanosin, Stavudin, Zalcitabin, Lamivudin, Abacavir, Amdoxovir, Elvucitabin, Alovudin, MIV-210, Racivir (±-FTC), D-d4FC, Phosphazid, Fozivudintidoxil, Apricitibin (AVX754), Amdoxovir, KP-1461 und Fosalvudintidoxil (formals HDP 99.0003),

4) die HIV-Nukleotid-Inhibitoren von reverser Transkriptase ausgewählt sind aus der Gruppe bestehend Tenofovir und Adefovir,

5) die HIV-Integrase-Inhibitoren ausgewählt sind aus der Gruppe bestehend aus Curcumin, Derivaten von Curcumin, Derivaten von Curcumin, Chicoriensäure, Derivaten von Chicoriensäure, 3,5-Dicafeoylchinasäure, Derivaten von 3,5-Dicafeoylchinasäure, Aurintricarbonsäure, Derivaten von Aurintricarbonsäure, Kaffeesäurephenethylester, Derivaten von Kaffeesäurephenethylester, Tyrphostin, Derivaten von Tyrphostin, Quercetin, Derivaten von Quercetin, S-1360, Zintevir (AR-177), L-870812, L-870810, MK-0518 (Raltegravir), Elvitegravir, BMS-538158, GSK364735C, BMS-707035, MK-2048 und BA 011,

6) der gp41-Inhibitor ausgewählt ist aus der Gruppe bestehend aus Enfuvirtid, Sifuvirtid, FB006M und TRI-1144,

7) es sich bei dem CXCR4-Inhibitor um AMD-070 handelt,

8) es sich bei dem Entry-Inhibitor um SP01A handelt,

9) es sich bei dem gp120-Inhibitor um BMS-488043 oder BlockAide/CR handelt,

10) es sich bei dem G6PD- und NADH-Oxydase-Inhibitor um Immunitin handelt,

11) die CCRS-Inhibitoren ausgewählt sind aus der Gruppe bestehend aus Aplaviroc, Vicriviroc, Maraviroc, PRO-140, INCB15050, PF-232798 (Pfizer) und CCR5mAb004,

12) die anderen Arzneimittel zur Behandlung von HIV ausgewählt sind aus der Gruppe bestehend aus BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (Bevirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (Ipilimumab), PBS 119, ALG 889 und PA-1050040 (PA-040),

13) die Interferone ausgewählt sind aus der Gruppe bestehend aus pegyliertem rIFN-α 2b, pegyliertem rIFN-α 2a, rIFN-α 2b, rIFN-α 2a, Konsensus-IFN-α (Infergen), Feron, Reaferon, Intermax α, rIFN-β, Infergen + Actimmun, IFN-ω mit DUROS, Albuferon, Locteron, Albuferon, Rebif, oralem Interferon α, IFN-α-2b XL, AVI-005, PEG-Infergen und pegyliertem IFN-β,

14) die Ribavirinanaloga ausgewählt sind aus der Gruppe bestehend aus Rebetol, Copegus und Viramidin (Taribavirin),

15) die NS5b-Polymerase-Inhibitoren ausgewählt sind aus der Gruppe bestehend aus NM-283, Valopicitabin, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554 und GSK625433,

16) der NS3-Protease-Inhibitor ausgewählt ist aus der Gruppe bestehend aus SCH-503034 (SCH-7), VX-950 (Telaprevir), BILN-2065, BMS-605339 und ITMN-191,

17) die α-Glucosidase-1-Inhibitoren ausgewählt sind aus der Gruppe bestehend aus MX-3253 (Celgosivir) und UT-231B,

18) die leberschützenden Mittel ausgewählt sind aus der Gruppe bestehend aus IDN-6556, ME 3738, LB-84451 und MitoQ,

19) die Nicht-Nukleosid-Inhibitoren von HCV ausgewählt sind aus der Gruppe bestehend aus Benzimidazolderivaten, benzo-1,2,4-Thiadiazinderivaten, Phenylalaninderivaten, A-831 und A-689 und

20) die anderen Arzneimittel zur Behandlung von HCV ausgewählt sind aus der Gruppe bestehnend aus Zadaxin, Nitazoxanid (Alinia), BIVN-401 (Virostat), PYN-17 (Altirex), KPE02003002, Actilon (CPG-10101), KRN-7000, Civacir, GI-5005, ANA-975, XTL-6865, ANA-971, NOV-205, Tarvacin, EHC-18, NIM811, DEBIO-025, VGX-410C, EMZ-702, AVI 4065, Bavituximab, Oglufanid und VX-497 (Merimepodib).

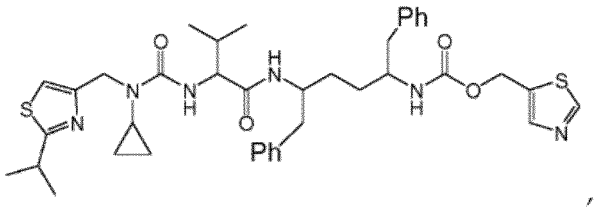
7. Verbindung nach Anspruch 1 oder 2 zur Verwendung in der Therapie.

8. Verbindung nach Anspruch 1 oder 2 zur Verwendung bei der Verbesserung der Pharmakokinetik eines Arzneimittels, das durch Cytochrom-P450-Monooxygenase metabolisiert wird, bei der Erhöhung des Blutplasmaspiegels eines Arzneimittels, das durch Cytochrom-P450-Monooxygenase metabolisiert wird, bei der Inhibierung von Cytochrom-P450-Monooxygenase, bei der Behandlung einer HIV-Infektion oder bei der Behandlung einer HCV-Infektion bei einem Patienten.

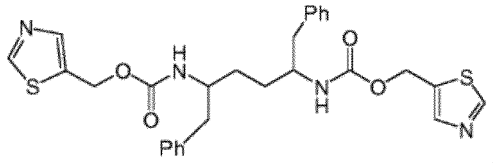
9. Verbindung zur Verwendung nach Anspruch 8, wobei es sich bei der Cytochrom-P450-Monooxygenase um Cytochrom-P450-Monooxygenase 3A handelt.

Revendications

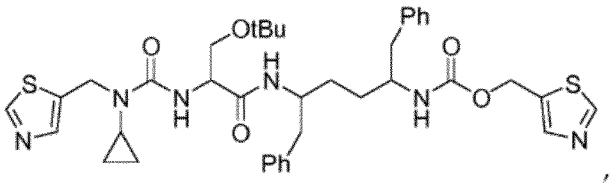
1. Composé de formule :



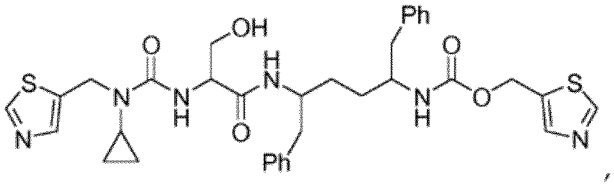
,



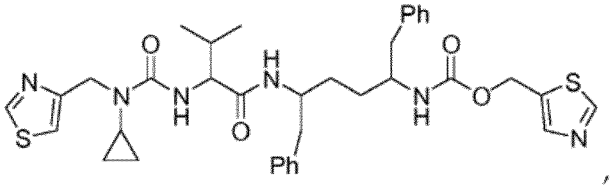
,



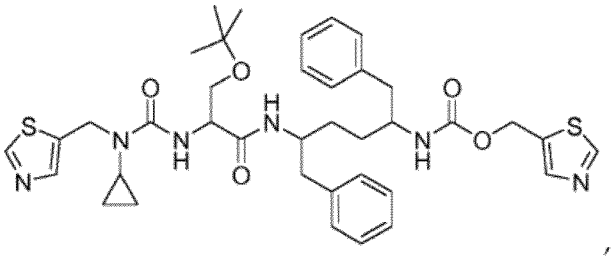
,



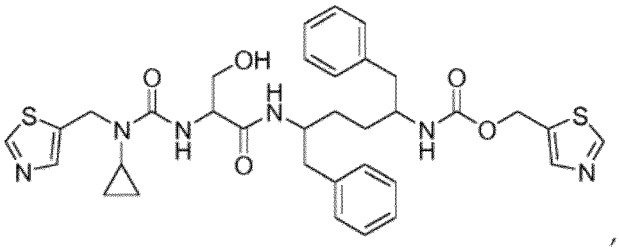
,



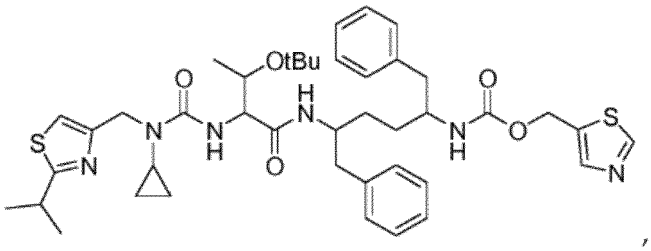
,



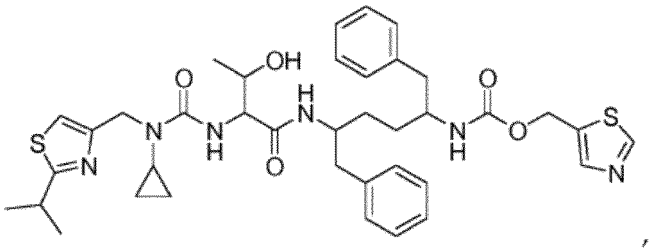
,



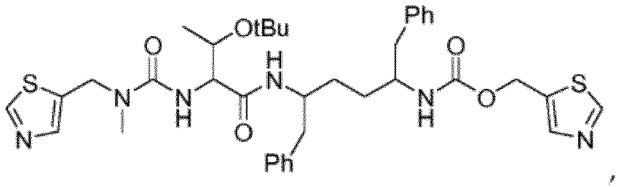
,



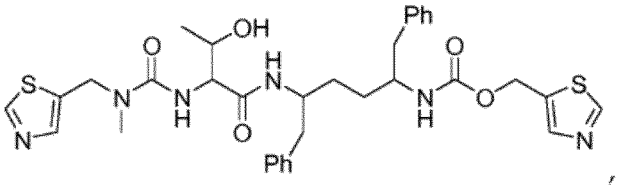
,



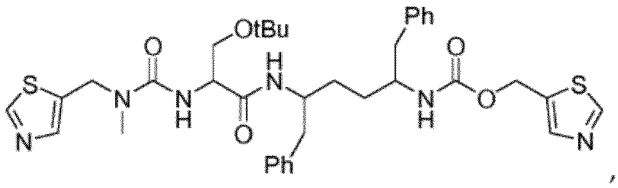
,



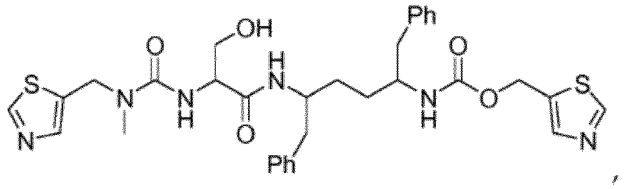
,



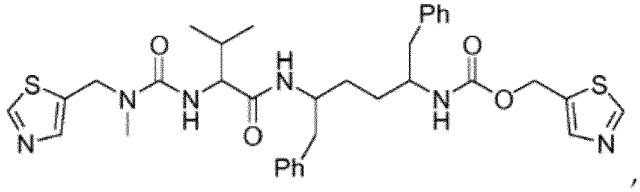
,



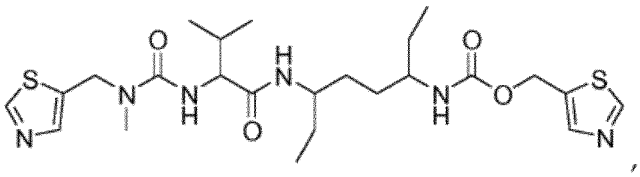
,



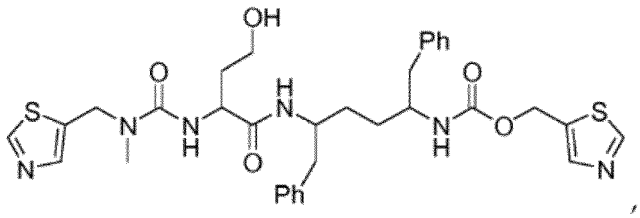
,



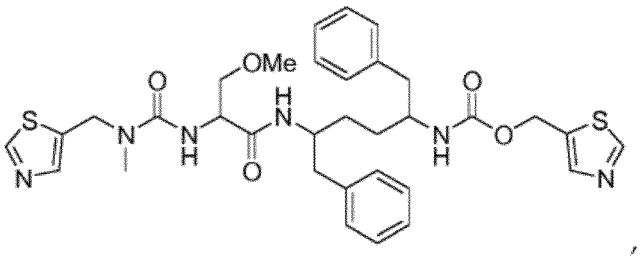
,



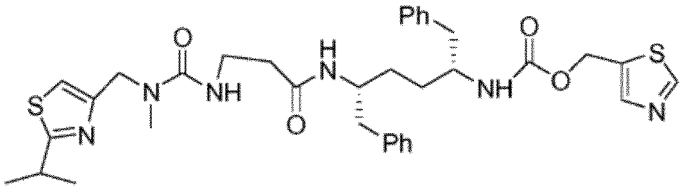
,

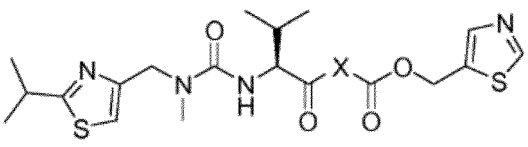


,

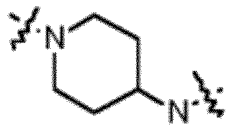


,

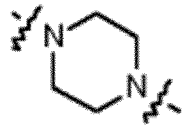


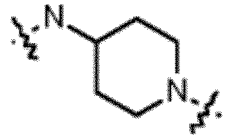


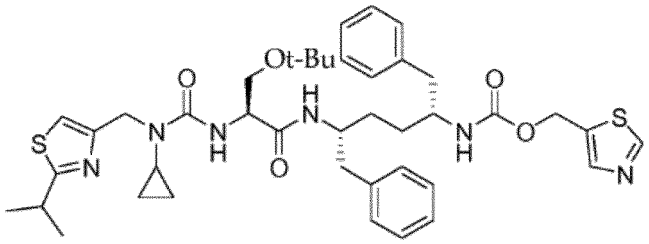
où X = $NH(CH_2)_2NH$ ou
X = $NH(CH_2)_3NH$ ou

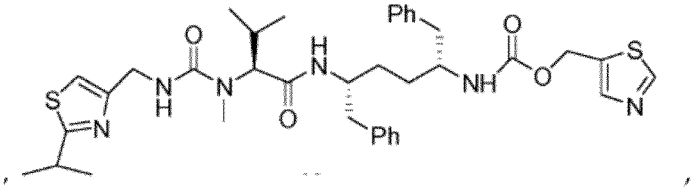


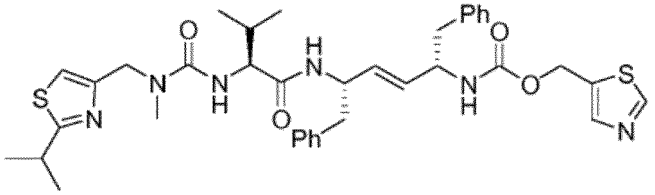
X =

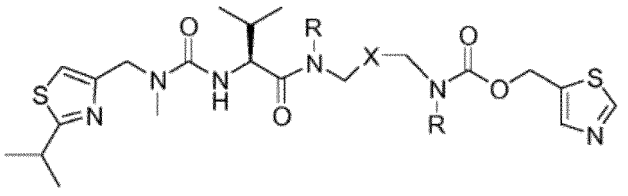




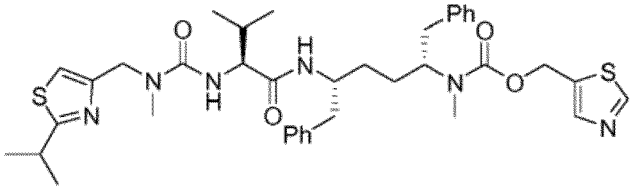




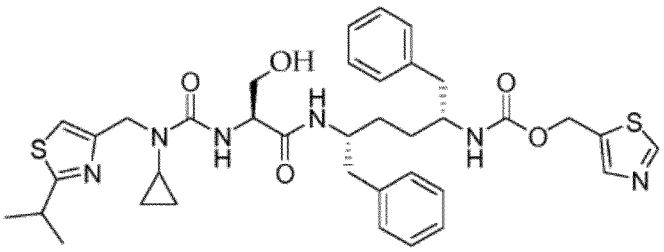




où X = CH_2, R = Bn

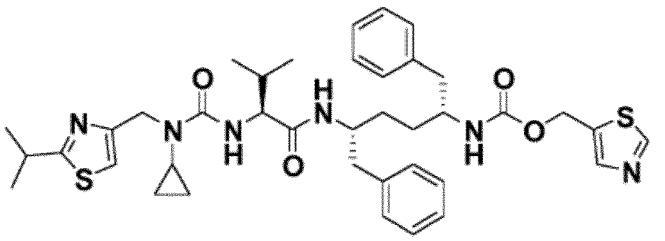


,

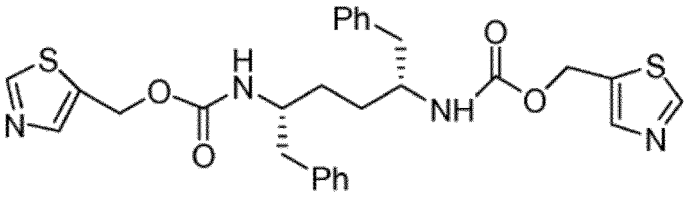


ou sel, solvate et/ou ester pharmaceutiquement acceptable de celui-ci.

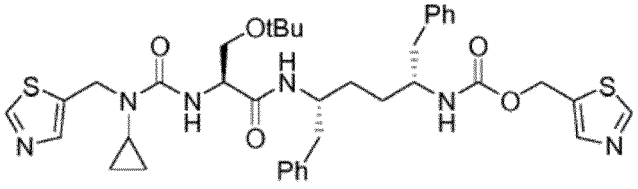
2. Composé selon la revendication 1, de formule :



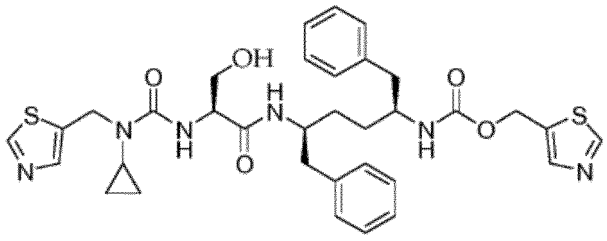
,



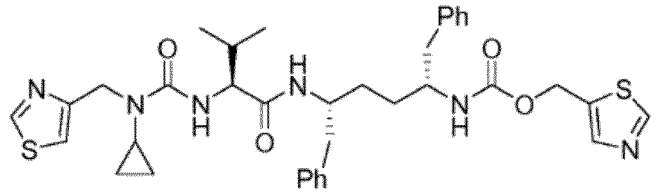
,



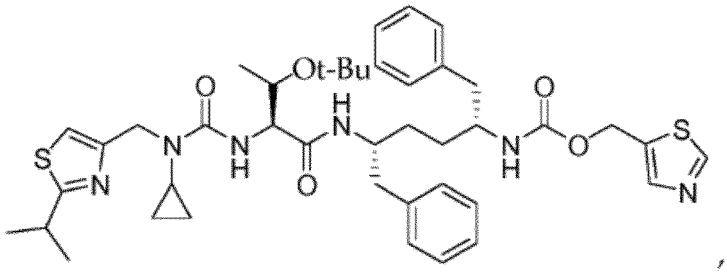
,



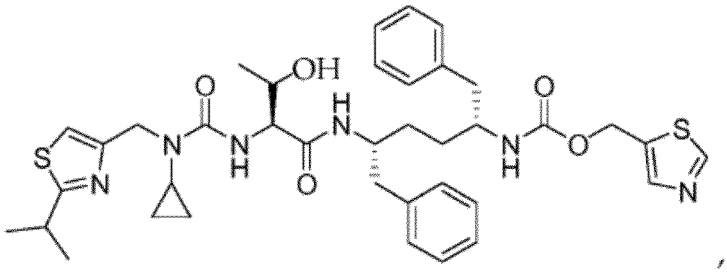
,



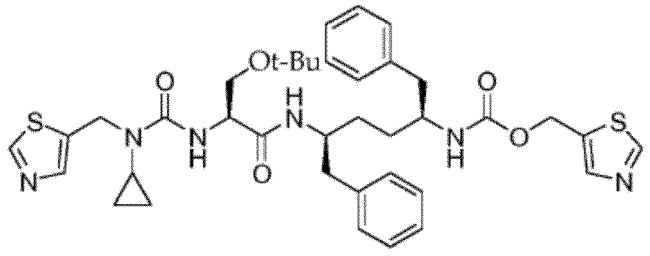
,



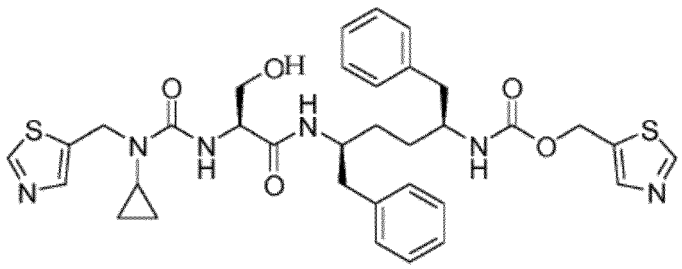
,



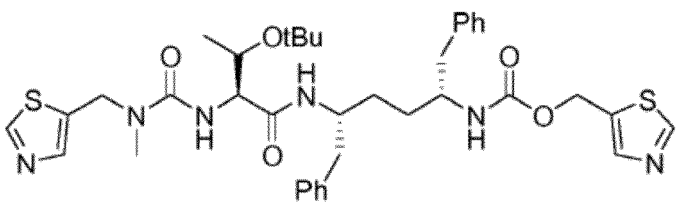
,



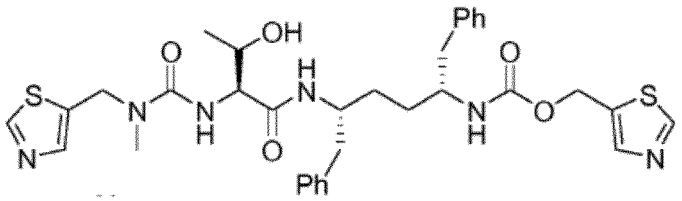
,

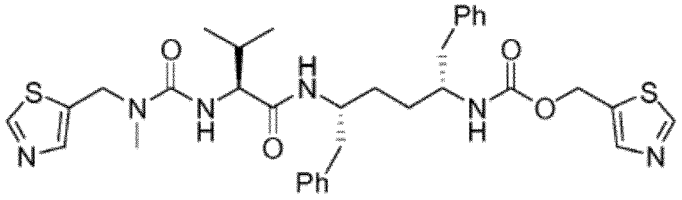


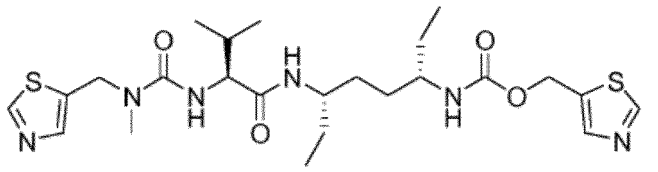
,

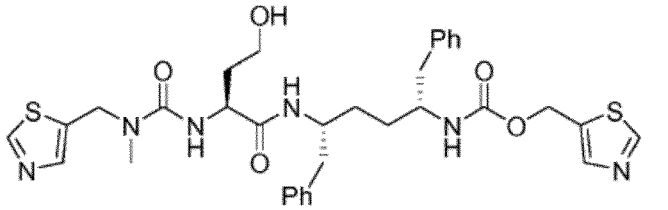


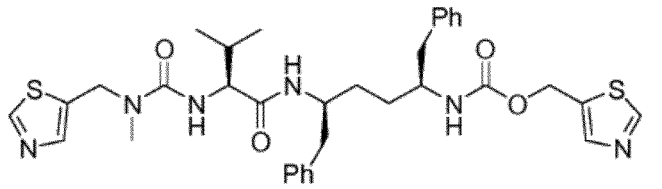
,

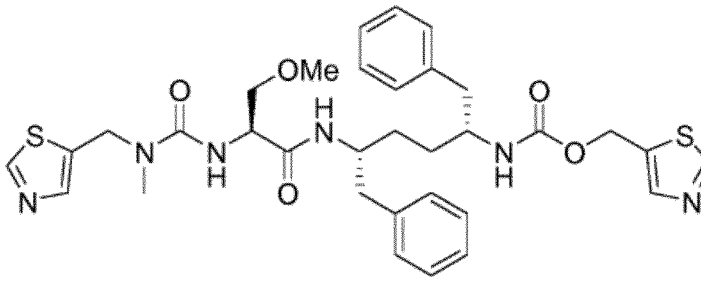












ou sel, solvate et/ou ester pharmaceutiquement acceptable de celui-ci.

3. Composition pharmaceutique comprenant un composé selon la revendication 1 ou 2, ou un de ses sels, solvates et/ou esters pharmaceutiquement acceptables, et un vecteur ou excipient pharmaceutiquement acceptable.

4. Composition pharmaceutique selon la revendication 3, comprenant en outre au moins un agent thérapeutique

supplémentaire qui est métabolisé par la cytochrome P450 monooxygénase, un ou plusieurs isozymes de P450, en particulier la cytochrome P450 monooxygénase 3A4.

5. Composition pharmaceutique selon la revendication 4, dans laquelle l'au moins un agent thérapeutique supplémentaire est choisi dans le groupe constitué de composés inhibiteurs de la protéase du VIH, d'inhibiteurs non nucléosidiques de la transcriptase inverse du VIH, d'inhibiteurs nucléosidiques de la transcriptase inverse du VIH, d'inhibiteurs de l'intégrase du VIH, d'inhibiteurs de gp41, d'inhibiteurs de CXCR4, d'inhibiteurs de gp120, d'inhibiteurs de CCR5, d'inhibiteurs de polymérisation de la capside, d'interférons, d'analogues de la ribavirine, d'inhibiteurs de la protéase NS3, d'inhibiteurs de l'α-glucosidase 1, d'hépatoprotecteurs, d'inhibiteurs non nucléosidiques du virus de l'hépatite C, d'autres médicaments pour le traitement de l'hépatite C, et de combinaisons de ceux-ci.

6. Composition pharmaceutique selon la revendication 5, dans laquelle :

1) lesdits inhibiteurs de la protéase du VIH sont choisis dans le groupe constitué de l'amprénavir, l'atazanavir, le fosamprénavir, l'indinavir, le lopinavir, le ritonavir, le nelfinavir, le saquinavir, le tipranavir, le brécanavir, le darunavir, le TMC-126, le TMC-114, le mozénavir (DMP-450), le JE-2147 (AG1776), le L-756423, le R00334649, le KNI-272, le DPC-681, le DPC-684, le GW640385X, le DG17, le PPL-100, le DG35 et l'AG 1859 ;
2) lesdits inhibiteurs non nucléosidiques de la transcriptase inverse du VIH sont choisis dans le groupe constitué de la capravirine, l'émivirine, la délaviridine, l'éfavirenz, la névirapine, la (+) calanolide A, l'étravirine, le GW5634, le DPC-083, le DPC-961, le DPC-963, le MIV-150 et le TMC-120, le TMC-278 (nilpivirène), le BILR 355 BS, le VRX 840773, l'UK-453061 et le RDEA806 ;
3) lesdits inhibiteurs nucléosidiques de la transcriptase inverse du VIH sont choisis dans le groupe constitué de la zidovudine, l'emtricitabine, la didanosine, la stavudine, la zalcitabine, la lamivudine, l'abacavir, l'amdoxovir, l'élvucitabine, l'alovudine, le MIV-210, le racivir ($\pm$-FTC), le D-d4FC, le phosphazide, la fozivudine tidoxil, l'apricitibine (AVX754), l'amdoxovir, le KP-1461 et la fosalvudine tidoxil (anciennement HDP 99.0003) ;
4) lesdits inhibiteurs nucléotidiques de la transcriptase inverse du VIH sont choisis dans le groupe constitué du ténofovir et de l'adéfovir ;
5) lesdits inhibiteurs de l'intégrase du VIH sont choisis dans le groupe constitué de la curcumine, de dérivés de la curcumine, de dérivés de la curcumine, de l'acide chicorique, de dérivés de l'acide chicorique, de l'acide 3,5-dicaféoylquinique, de dérivés de l'acide 3,5-dicaféoylquinique, de l'acide aurintricarboxylique, de dérivés de l'acide aurintricarboxylique, de l'ester phénéthylique de l'acide caféique, de dérivés de l'ester phénéthylique de l'acide caféique, de la tyrphostine, de dérivés de la tyrphostine, de la quercétine, de dérivés de la quercétine, du S-1360, du zintévir (AR-177), du L-870812, du L-870810, du MK-0518 (raltégravir), de l'élvitégravir, du BMS-538158, du GSK364735C, du BMS-707035, du MK-2048 et du BA 011 ;
6) lesdits inhibiteurs de gp41 sont choisis dans le groupe constitué de l'enfuvirtide, du sifuvirtide, du FB006M et du TRI-1144 ;
7) ledit inhibiteur du CXCR4 est l'AMD-070 ;
8) ledit inhibiteur d'entrée est le SP01A ;
9) lesdits inhibiteurs de gp120 sont BMS-488043 ou BlockAide/CR ;
10) ledit inhibiteur de G6PD et de la NADH-oxydase est l'immunitine ;
11) lesdits inhibiteurs de CCR5 sont choisis dans le groupe constitué de l'aplaviroc, du vicriviroc, du maraviroc, du PRO-140, de l'INCB15050, du PF-232798 (Pfizer) et du CCR5mAb004 ;
12) lesdits autres médicaments pour le traitement du VIH sont choisis dans le groupe constitué de BAS-100, SPI-452, REP 9, SP-01A, TNX-355, DES6, ODN-93, ODN-112, VGV-1, PA-457 (bévirimat), Ampligen, HRG214, Cytolin, VGX-410, KD-247, AMZ 0026, CYT 99007A-221 HIV, DEBIO-025, BAY 50-4798, MDX010 (ipilimumab), PBS 119, ALG 889 et PA-1050040 (PA-040) ;
13) lesdits interférons sont choisis dans le groupe constitué de rIFN-α 2b pégylé, rIFN-α 2a pégylé, rIFN-α 2b, rIFN-α 2a, IFN-α consensus (infergen), féron, réaféron, intermax α, rIFN-β, infergen + actimmune, IFN-ω avec DUROS, albuféron, loctéron, Albuféron, Rebif, interféron α oral, IFN-α-2b XL, AVI-005, PEG-Intergen et IFN-β pégylé ;
14) lesdits analogues de la ribavirine sont choisis dans le groupe constitué du rébétol, du copégus et de la viramidine (taribavirine) ;
15) lesdits inhibiteurs de la polymérase NS5b sont choisis dans le groupe constitué de NM-283, valopicitabine, R1626, PSI-6130 (R1656), HCV-796, BILB 1941, XTL-2125, MK-0608, NM-107, R7128 (R4048), VCH-759, PF-868554 et GSK625433 ;
16) lesdits inhibiteurs de la protéase NS3 sont choisis dans le groupe constitué de SCH-503034 (SCH-7), VX-950 (télaprévir), BILN-2065, BMS-605339 et ITMN-191 ;
17) lesdits inhibiteurs de l'α-glucosidase 1 sont choisis dans le groupe constitué de MX-3253 (celgosivir) et UT-

231B ;
18) lesdits hépatoprotecteurs sont choisis dans le groupe constitué d'IDN-6556, ME 3738, LB-84451 et MitoQ ;
19) lesdits inhibiteurs non nucléosidiques du virus de l'hépatite C sont choisis dans le groupe constitué de dérivés de la benzimidazole, de dérivés de la benzo-1,2,4-thiadiazine, de dérivés de la phénylalanine, d'A-831 et d'A-689 ; et
20) lesdits autres médicaments pour le traitement de l'hépatite C sont choisis dans le groupe constitué de la zadaxine, du nitazoxanide (alinia), du BIVN-401 (virostat), du PYN-17 (altirex), du KPE02003002, de l'actilon (CPG-10101), du KRN-7000, du civacir, du GI-5005, de l'ANA-975, du XTL-6865, de l'ANA-971, du NOV-205, de la tarvacine, de l'EHC-18, du NIM811, du DEBIO-025, du VGX-410C, de l'EMZ-702, de l'AVI 4065, du Bavituximab, de l'Oglufanide et du VX-497 (mérimépodib).

7. Composé selon la revendication 1 ou 2 pour utilisation en thérapie.

8. Composé selon la revendication 1 ou 2 pour utilisation dans l'amélioration de la pharmacocinétique d'un médicament métabolisé par la cytochrome P450 monooxygénase, l'augmentation du niveau plasmatique d'un médicament métabolisé par la cytochrome P450 monooxygénase, l'inhibition de la cytochrome P450 monooxygénase, le traitement d'une infection par le VIH ou le traitement d'une infection par le virus de l'hépatite C chez un patient.

9. Composé destiné à être utilisé selon la revendication 8, la cytochrome P450 monooxygénase étant la cytochrome P450 monooxygénase 3A.

REFERENCES CITED IN THE DESCRIPTION

This list of references cited by the applicant is for the reader's convenience only. It does not form part of the European patent document. Even though great care has been taken in compiling the references, errors or omissions cannot be excluded and the EPO disclaims all liability in this regard.

Non-patent literature cited in the description

- **PAQUETTE, LEO A. ; W.A. BENJAMIN.** Principles of Modern Heterocyclic Chemistry. 1968 **[0032]**
- The Chemistry of Heterocyclic Compounds, A Series of Monographs. John Wiley & Sons, 1950, vol. 13, 14, 16, 19, 28 **[0032]**
- *J. Am. Chem. Soc.,* 1960, vol. 82, 5566 **[0032]**
- McGraw-Hill Dictionary of Chemical Terms. McGraw-Hill Book Company, 1984 **[0048]**
- **ELIEL, E. ; WILEN, S.** Stereochemistry of Organic Compounds. John Wiley & Sons, Inc, 1994 **[0048]**
- **THEODORA W. GREENE ; PETER G. M. WUTS.** Protective Groups in Organic Synthesis. John Wiley & Sons, Inc, 1999 **[0052] [0185] [0205]**
- **KOCIENSKI, PHILIP J.** Protecting Groups. Georg Thieme Verlag Stuttgart, 1994 **[0052]**
- Protecting Groups: An Overview. 1-20 **[0052]**
- Hydroxyl Protecting Groups. 21-94 **[0052]**
- Diol Protecting Groups. 95-117 **[0052]**
- Carboxyl Protecting Groups. 118-154 **[0052]**
- Carbonyl Protecting Groups. 155-184 **[0052]**
- *J. Med. Chem.,* 1998, vol. 41, 602 **[0141] [0148] [0149]**
- *J. Org. Chem.,* 1994, vol. 59, 1937 **[0143] [0150]**
- *Tetrahedron,* 1997, vol. 53, 4769 **[0155]**
- *J. Org. Chem.,* 1987, vol. 52, 3759 **[0156]**
- *J. Org. Chem,* 1996, vol. 61, 444 **[0181]**
- *J. Org. Chem.,* 1996, vol. 61, 444-450 **[0201]**
- *J. Med. Chem,* 1993, vol. 36, 1384 **[0225]**
- **LING, K.-H.J. et al.** *Drug Metab. Dispos.,* 1995, vol. 23, 631-636 **[0463]**
- **JURIMA-ROMET et al.** *Drug Metab. Dispos.,* 1994, vol. 22, 849-857 **[0463]**
- **LEEMAN, T. et al.** *Life Sci.,* 1992, vol. 52, 29-34 **[0465]**
- **M.V. TOTH ; G.R.MARSHALL.** *Int. T. Peptide Protein Res.,* 1990, vol. 36, 544 **[0467] [0470]**
- **ERMOLIEFF J. ; LIN X. ; TANG J.** *Biochemistry,* 1997, vol. 36, 12364 **[0469]**
- **WEISLOW OS ; KISER R ; FINE DL ; BADER J ; SHOEMAKER RH ; BOYD MR.** *J. Natl. Cancer Inst.,* 1989, vol. 81, 577 **[0473] [0477]**